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Research Article

Association of Lesion Location with Post-Stroke Depression in China: A Systematic Review and Meta-Analysis

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Abstract

Background: Post-stroke depression (PSD) is a mental health condition that can develop after a stroke, with a higher risk of death and negative outcomes. However, limited research has explored how PSD incidence relates to brain locations in Chinese patients. This study aims to fill this gap by examining the link between PSD occurrence and brain lesion location, as well as the type of stroke experienced by the patient.

Methods: We conducted a systematic search in databases to gather post-stroke depression literature published between January 1, 2015 and May 31, 2021. Following this, we performed a meta-analysis using RevMan to analyze the incidence of PSD associated with different brain regions and types of stroke separately.

Results: We analyzed seven studies, with a total of 1604 participants. Our findings indicated that the incidence of PSD was higher when the stroke occurred in the left hemisphere compared to the right hemisphere (RevMan: $Z = 8.93$, $P < 0.001$, $OR = 2.69$, 95% CI: 2.16 – 3.34, fixed model); PSD was more common when the stroke affected the cerebral cortex rather than the subcerebral cortex (RevMan: $Z = 3.96$, $P < 0.001$, $OR = 2.00$, 95% CI: 1.42 – 2.81) and when it affected the anterior cortex compared to the posterior cortex (RevMan: $Z = 3.85$, $P < 0.001$, $OR = 1.89$, 95% CI: 1.37 – 2.62). However, we did not find a significant difference in the occurrence of PSD between ischemic and hemorrhagic strokes (RevMan: $Z = 0.62$, $P = 0.53$, $OR = 0.02$, 95% CI: -0.05 – 0.09).

Conclusion: Our findings revealed a higher likelihood of PSD in the left hemisphere, specifically in the cerebral cortex and anterior region.

Keywords: *Lesion Location; Post-Stroke Depression; Cortex; Systematic Review*

Introduction

Stroke is an acute cerebrovascular event characterized by a sudden loss of blood supply to the brain. Recent studies have established a link between stroke and various neuropsychiatric disorders, such as depression and anxiety [1,2]. Post-stroke depression (PSD), as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is defined as depression caused by stroke. The first study reporting PSD was published in 1955 [3] and since then, numerous publications have investigated this condition [4-6]. A meta-analysis involving 15,573 stroke patients revealed that PSD has a point incidence rate of up to 33.5% [7]. Additionally, PSD has been linked to increased mortality rates. For instance, in China, stroke was responsible for 1.57 million deaths in 2018, with a mortality rate of 149.49 per 100,000 [8]. A ten-year follow-up cohort study in the United States showed that PSD patients had 3.4 times higher mortality rates, independent of age, sex, social class, type of stroke, lesion location, and level of social functioning [9].

Recent studies have identified stroke characteristics and lesion location as risk factors for developing PSD [7,10]. A meta-analysis conducted by Mitchell., *et al*. [7] found that the risk of depressive disorder was significantly associated with left (dominant) hemisphere stroke. Another meta-analysis by Douven., *et al*. [10], which included 74 studies on PSD, revealed that 23% of the studies reported frontal lesion location as being linked to PSD, while 8% of the studies found subcortical lesion location to be associated with PSD. Notably, most of the research has been conducted in Western countries, such as the United States and Australia. Thus, there is a lack of studies investigating the relationship between PSD incidence and lesion locations in Chinese patients. Further research is needed to bridge this knowledge gap.

This article presented a review of published research articles that investigated the relationship between PSD and its risk factors, specifically lesion location and type, in the Chinese population between 2015 and 2020. Our aim was to contribute to the understanding of PSD for early identification, effective treatment, and improved prognoses in China. This work holds significant importance in the field of stroke rehabilitation and mental health research.

Materials and Methods

Search strategy and selection criteria

This study's review protocol has been officially registered with PROSPERO under the reference number CRD42016049179. As a review study, ethics approval was not deemed necessary. To ensure a rigorous and structured approach to the systematic review and meta-analysis, this study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines, as evidenced by the S1 PRISMA Checklist.

From January 1, 2015, to May 31, 2021, we conducted a literature review on post-stroke depression in China. The databases searched were China National Knowledge Infrastructure (CNKI), Wanfang Data Journal Full-text Database, Weipu Chinese Sci-tech Periodical Database, PubMed, and Cochrane Library.

Our search strategy involved querying English and Chinese databases with specific keywords. In the English databases, the keywords "stroke," "depression," "lesion location," and "in China" were combined with the Boolean operator "AND." Articles related to PSD were retrieved and reviewed. In addition, we searched for further relevant literature within the retrieved articles that might satisfy our inclusion criteria. A similar search strategy was implemented in the Chinese databases, using the keywords 抑郁, 卒中, 位置, and 部位, and articles related to PSD were also obtained.

The included studies in this review were required to meet several criteria. Firstly, they had to be peer-reviewed and employ cross-sectional, case-control, or cohort study designs. Secondly, they needed to provide clear diagnostic criteria for both stroke and depression and evaluation tools within the study. Additionally, the study subjects' general data needed to be presented comprehensively, along with the precise start and end times of their treatment. The criteria for inclusion, exclusion, and lesion location also needed to be clearly stated.

If the article was published in both a journal and a conference, only the journal data were considered. Ethics approval from the appropriate committee and informed consent from the subjects, either written or verbal, were also required. Finally, the study had to report the incidence of depression among patients after stroke, based on left or right hemisphere, ischemia or hemorrhage stroke, and cortex or subcortex posterior cerebral stroke. In summary, the PICOS-based inclusion criteria were population (patients after stroke), intervention (left hemisphere stroke, ischemia stroke, cortex stroke, or anterior cerebral stroke), comparison (right hemisphere stroke, hemorrhage stroke, subcortex stroke, or posterior cerebral stroke), outcome (incidence of depression), and study design (case-control study or cohort study).

This study has established the following exclusion criteria: (1) the presence of incomplete, unclear, misleading, or contentious data; (2) the use of animal models as the research subjects; (3) inclusion in the literature as a review, conference notice, or commentary; and (4) missing data.

Literature screening

In the first stage of screening, we evaluated the title and abstract of the document. Following this, a second screening was conducted where we carefully examined the full text of each article. Our final selection was made based on adherence to our predetermined selection criteria.

In the context of stroke localization, it is recommended that the literature incorporates the utilization of cranial CT or MRI. To objectively classify the type of stroke, we proposed the Ratio calculation: the ratio of the shortest distance between the frontal pole and the forefront of the lesion to the total length of the occipital pole. A ratio of less than 40% indicated an anterior cerebral stroke, while a ratio of more than 40% indicated a posterior cerebral stroke [11-13].

The diagnosis of depression was made in accordance with the Chinese Diagnostic and Classification Standards for Mental Disorders, 3rd edition, the American Mental Disorder Classification and Diagnosis Standards Fourth Edition (DSM-IV), and the American Mental Disorders, and Classification and Diagnostic Criteria Fifth Edition (DSM-5). Assessment tools employed for depression included the Hamilton Depression Scale (HAMD), the Depression Self-Rating Scale (SDS), and other relevant scales.

The entire process was independently conducted by two researchers. In the event of any disagreement, the researchers held further discussions to determine the inclusion of the article in question.

Data extraction and quality assessment

The included literature was independently evaluated by two investigators concurrently. In cases where a disagreement arose, a third investigator intervened to make a decision after further discussion. Relevant data, including the incidence of PSD, as well as the location of the stroke (categorized by left/right hemisphere, ischemic and hemorrhagic stroke, cortex and subcortex, and anterior and posterior cerebral stroke), were extracted.

The Newcastle-Ottawa Scale (NOS) was developed by the Universities of Newcastle, Australia and Ottawa, Canada to assess the quality of nonrandomized studies in meta-analysis [14]. In the current meta-analysis, the NOS scale was adopted to evaluate the evidence levels. The NOS rating scale is a standardized tool for quality evaluation [14], with a perfect score of 9 points. A higher score is indicative of better article quality.

Statistical analysis

Meta-analysis was performed using Review Manager 5.3 software, with pooled estimates calculated through a random-effects model. Unadjusted odds ratios (ORs) were calculated using raw data. Meta-analysis was conducted to explore the relationships between PSD and the following covariates: left/right hemisphere, ischemic and hemorrhagic stroke, cortex and subcortex, as well as anterior and posterior cerebral stroke. Prior to this, heterogeneity testing was conducted (using P values and I^2 values) to determine the degree of homogeneity or heterogeneity among the included documents. P-values greater than 0.05 or I^2 values less than 0.25 indicated homogeneity, while P-values less than 0.05 or I^2 values greater than 0.25 suggested heterogeneity. The presence of publication bias was investigated using Begg's test in Stata 14 software [15].

Results

The basic information

From January 1, 2015 to May 31, 2021, a total of 144 articles were initially retrieved, including 141 in Chinese and 3 in English. After excluding 94 duplicated reports, a total of 50 articles were subjected to title and abstract screening, resulting in the exclusion of 43 articles, including 2 reviews, 1 animal study, and 1 study that did not match the article types. The full texts of 46 studies were then assessed for the next stage of selection, which led to the exclusion of 39 studies with insufficient information. Ultimately, 7 articles, with a combined total of 1604 patients, were identified and included based on the established criteria (Figure 1). The diagnosis criteria for depression were based on the HAMD scale in 6 studies [16-21], the Chinese Diagnostic and Classification Standards for Mental Disorders, 3rd edition, in 1 study [13] and the Depression Self-Rating Scale (SDS) in another study [11]. The included articles had a minimum score of 7 on the NOS scale.

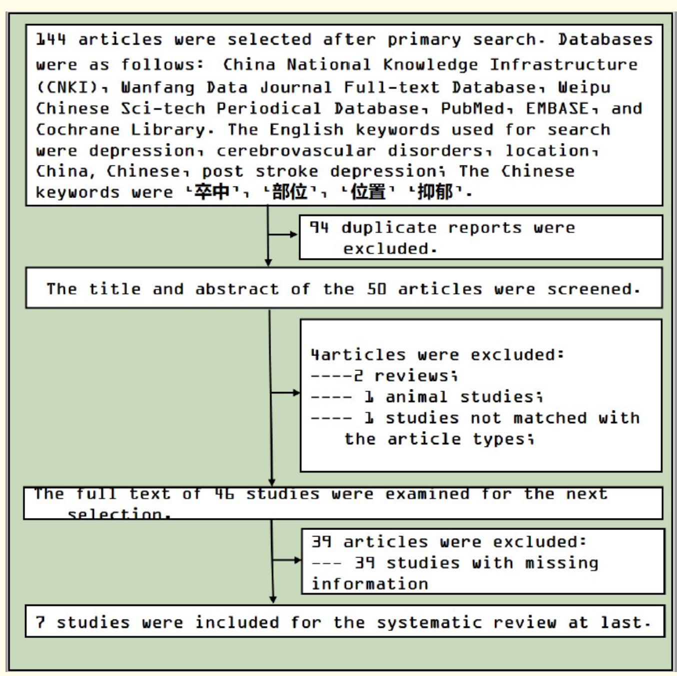

***Figure 1**: Flow chart of the study.*

Meta-Analysis of the incidence of PSD between left and right hemispheres (See figure 2)

The literature review included a comparison of PSD incidence caused by left and right hemisphere stroke in seven articles. Among 666 cases of left hemisphere stroke, 321 were diagnosed with PSD, while 266 out of 938 cases of right hemisphere stroke were diagnosed with

PSD. The occurrence of PSD in patients with left hemisphere stroke was higher than that of right hemisphere stroke (RevMan: Z = 8.93, P < 0.001, OR = 2.69, 95% CI: 2.16 - 3.34, fixed model). The included studies demonstrated no heterogeneity (P = 0.58, I^2 = 0.0%). A forest plot detailing the meta-analysis is provided in figure 2.

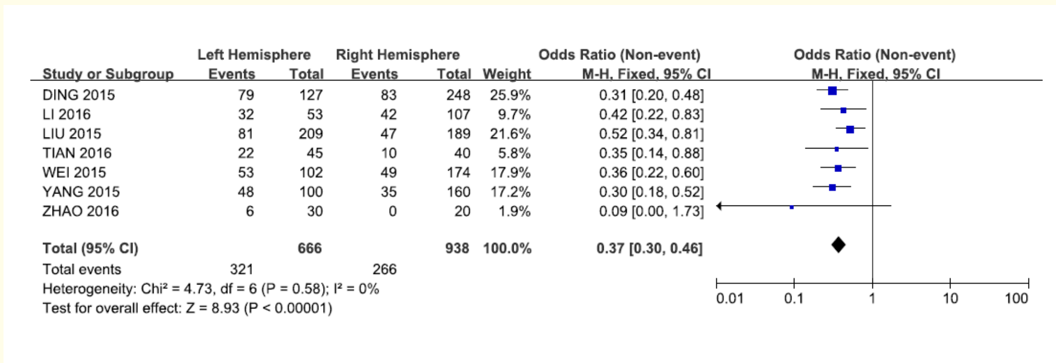

Figure 2: *Meta-Analysis of the incidence of PSD between left and right hemisphere.*

The Begg's test showed no indication of publication bias in the total samples (P = 0.327), while the Begg's funnel plot is illustrated in figure 3.

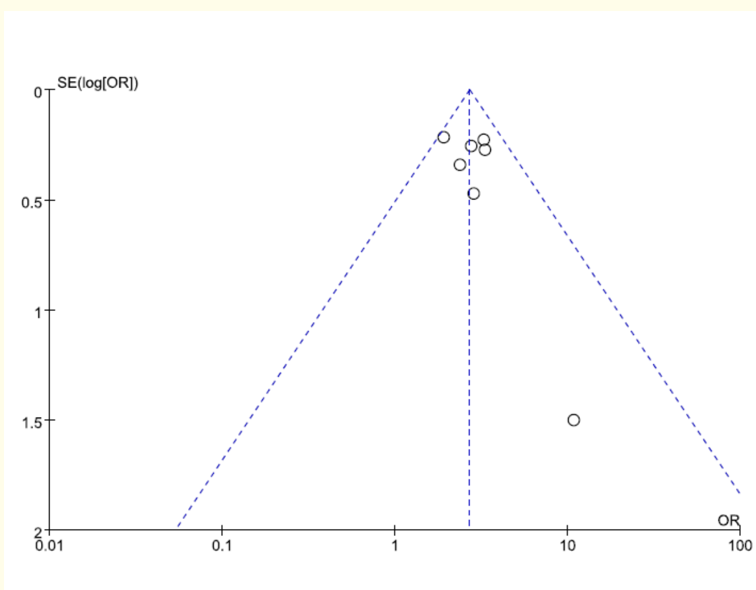

Figure 3: *Begg's funnel plot for the Meta-Analysis of the incidence of PSD between left and right hemisphere.*

Meta-analysis of the incidence of PSD between ischemia and hemorrhage stroke (See figure 4)

In comparing the incidence of PSD between ischemic and hemorrhagic stroke, we analyzed three articles (ischemic stroke n = 537, hemorrhagic stroke n = 304) [17,18,22]. Our analysis demonstrated that the occurrence of PSD in ischemic stroke was not significantly different from that in hemorrhagic stroke (RevMan: Z = 0.62, P = 0.53, OR = 0.02, 95% CI: -0.05 - 0.09, fixed model). Moreover, we found no heterogeneity within the included studies (P = 0.78, I^2 = 0%). Begg's test further supported this finding by showing no evidence of publication bias within the total sample (P = 0.521). The Begg's funnel plot is illustrated in figure 5.

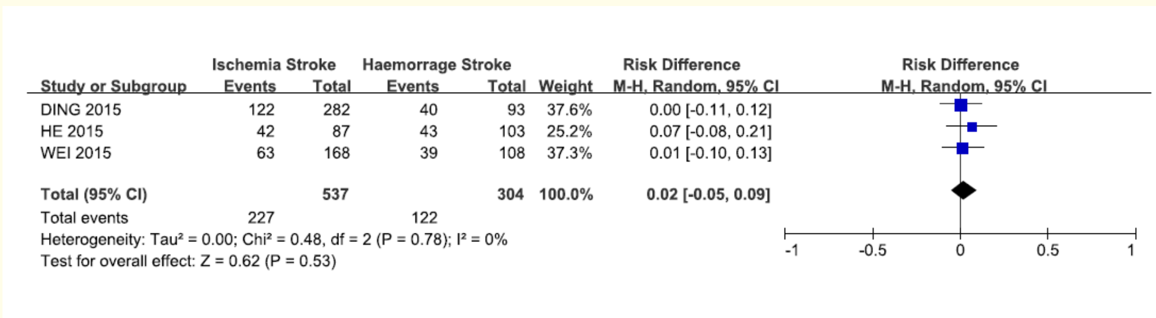

Figure 4: *Meta-Analysis of the incidence of PSD between ischemia and hemorrhage stroke.*

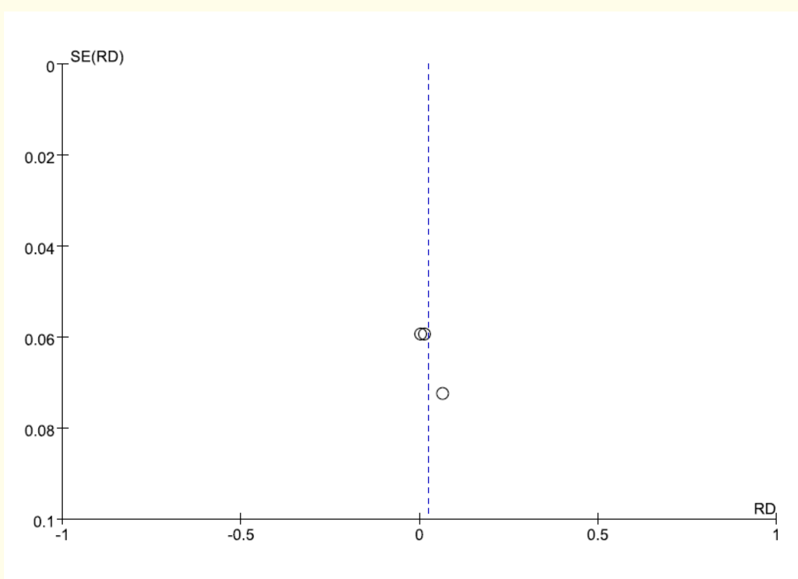

Figure 5: *Begg's funnel plot for the Meta-Analysis of the incidence of PSD between ischemia and hemorrhage stroke.*

Meta-analysis of the incidence of PSD between cortex and subcortex (See figure 6)

We analyzed the incidence of PSD caused by cortex and subcortex stroke using three relevant articles [11,13,19]. Of the 276 cases of cortex stroke, 120 were diagnosed with PSD, while of the 329 cases of subcortex stroke, 94 were diagnosed with PSD. Our findings revealed a higher incidence of PSD caused by cerebral cortex than subcerebral cortex (RevMan: Z = 3.96, P < 0.001, OR = 2.00, 95% CI: 1.42 - 2.81, fixed model). There was no heterogeneity observed among the included studies (P = 0.10, I^2 = 57%). The meta-analysis forest plot is depicted in figure 6. Begg's test further demonstrated no evidence of publication bias within the total sample (P = 0.438). The Begg's funnel plot is shown in figure 7.

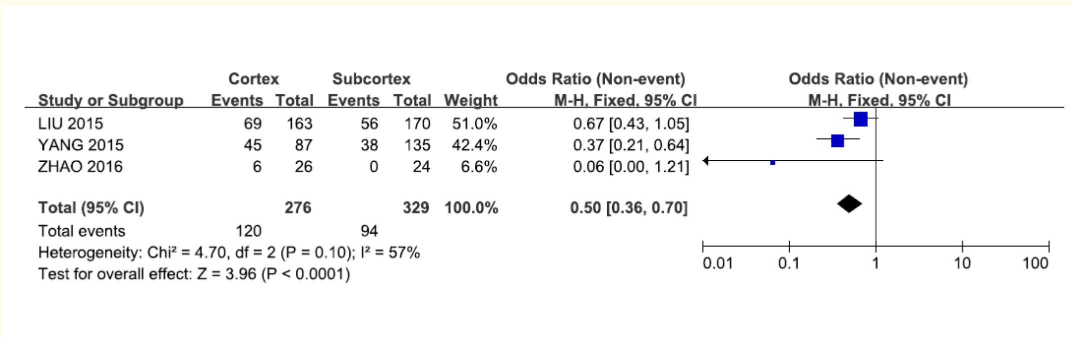

Figure 6: *Meta-Analysis of the incidence of PSD between cerebral and subcerebral cortex.*

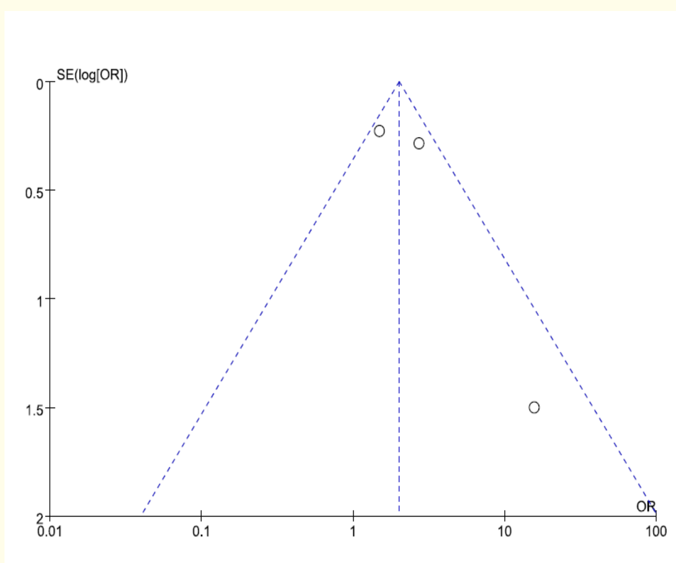

Figure 7: *Begg's funnel plot for the Meta-Analysis of the incidence of PSD between cerebral and subcerebral cortex.*

Meta-analysis of the incidence of PSD caused by anterior and posterior cerebral stroke (See figure 8)

We analyzed three articles to compare the incidence of PSD caused by anterior and posterior cerebral stroke [11,13,19]. Of the 421 cases of anterior stroke, 137 were diagnosed with PSD, whereas 79 out of 373 cases of posterior stroke had PSD. Our analysis showed that the occurrence of PSD caused by anterior cortex was significantly higher than that caused by the posterior cortex (RevMan: $Z = 3.85$, $P < 0.001$, OR = 1.89, 95% CI: 1.37 - 2.62, fixed model). Moreover, we found no heterogeneity within the included studies ($P = 0.34$, $I^2 = 6\%$), and the meta-analysis forest plot is shown in figure 8.

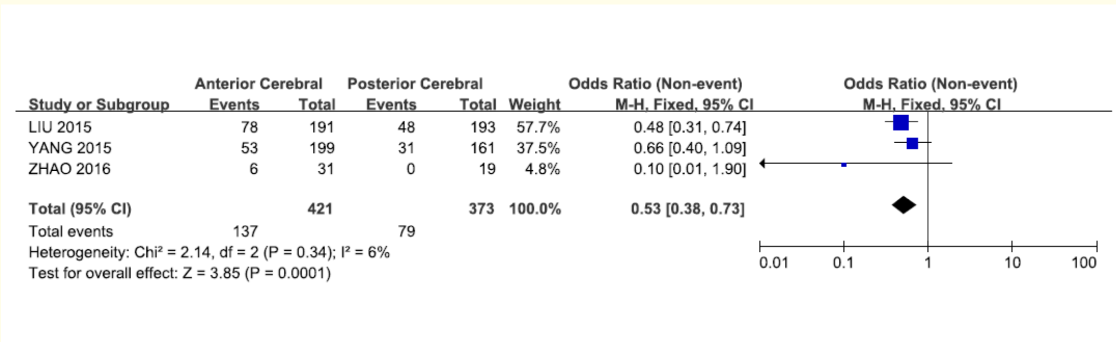

Figure 8: *Meta-Analysis of the incidence of PSD between anterior and posterior cortex.*

Begg's test further supported our analysis, showing no evidence of publication bias in the total sample ($P = 0.438$). The Begg's funnel plot is illustrated in figure 9.

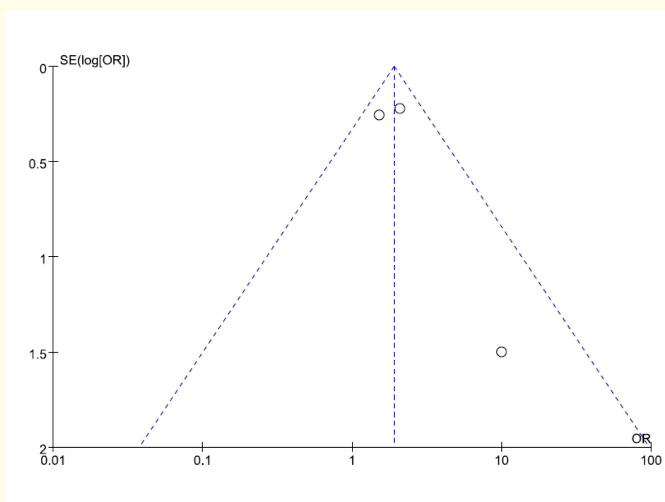

Figure 9: *Begg's funnel plot for the Meta-Analysis of the incidence of PSD between anterior and posterior cortex.*

Discussion

This meta-analysis employed the Newcastle-Ottawa Scale (NOS), a case-control evaluation scale, to assess the quality of the included articles. The selected articles scored between 7 and 8 points, indicating high quality. Our study included 7 qualified literatures, with patients recruited from 7 distinct regions in China, indicating sample representativeness.

Our findings revealed a significant association between PSD and left hemisphere stroke in the Chinese population. This result is consistent with the study conducted by Mitchell., *et al*. which included 146 citations and reported a higher PSD rate (34.3%, 95% CI= 24.8% to 44.4%) in left hemisphere stroke [7]. Therefore, left hemisphere stroke may be considered a risk factor for PSD.

We did not observe a significant difference in PSD occurrence between ischemic and hemorrhagic stroke, as both conditions reduce blood supply and lead to neuron necrosis or apoptosis [23]. However, hematoma formation in hemorrhagic stroke can also cause reduced blood flow by compressing the surrounding brain tissue.

We defined Lesion location ratio (LLR) as the shortest distance between the stroke lesion's foremost part and the frontal pole, divided by the total distance between the frontal and occipital poles. An LLR of less than 40% was classified as the anterior part of the brain, and more than 40% as the posterior part. Our meta-analysis demonstrated that stroke in the anterior part of the brain was significantly associated with PSD. Previous studies have shown that abnormal connectivity with the anterior part of the brain, such as the anterior default network [24], is related to major depressive disorder. Using global signal regression (GBCr) values - calculated as the average of correlations between each voxel and all other gray matter voxels in the brain - MDD patients displayed reduced GBCr in the anterior region of the brain. Additionally, seed-based analyses revealed dysconnectivity between the anterior region and the rest of the brain in MDD patients [25]. The findings from the UK Biobank in the Human Connectome Project, which included 1017 participants, further demonstrated that depressive symptoms were significantly related to the anterior part of the brain. Specifically, the prefrontal cortex and anterior cingulate cortex showed increased functional connectivity in individuals with depressive symptoms [26].

The cerebral cortex, the outermost layer of the cerebrum, plays a crucial role in neural integration in the central nervous system. The axons from the cerebral cortex reach subcortical structures, including the basal ganglia, limbic system, and diencephalon. Both cortex and subcortex parts of the brain have been implicated in the pathogenesis of depression [25,27]. Chronic mild stress depression animal models showed significant alterations in the frontal cortex, but not the hippocampus [28]. Prefrontal cortex, in particular, may be significantly related to depressive symptoms [29,30].

Limitations of the Study

There are several limitations to our study that should be acknowledged. Firstly, our inclusion criteria were rigorous, which resulted in the inclusion of only seven studies. Secondly, we were unable to investigate the association between stroke and depression in patients from western countries. Lastly, the current review only included studies that were published, and ongoing studies were not taken into account.

Implications

PSD is a common complication that arises secondary to stroke. It is characterized by symptoms such as depressed mood, decreased interest, slower thinking, and reduced activity [31]. Despite its prevalence, PSD is often overlooked by family members and doctors, resulting in delayed recognition, diagnosis, and treatment [32]. The prognosis of stroke and PSD has a significant impact on the quality of life of patients. Previous research suggests that the location of stroke may play a significant role in the development of PSD [33]. Therefore, it is essential to identify which positions and types of stroke are most significantly associated with PSD. Our findings reveal that the incidence of PSD is significantly associated with left hemisphere, anterior, and cortex stroke. This information is valuable for both psychiatrists and neurologists in the diagnosis and management of PSD in stroke patients.

Conclusion

Our findings revealed a higher likelihood of PSD in the left hemisphere, specifically in the cerebral cortex and anterior region.

Conflict of Interest Statement

None.

Author Contribution

XQ. L., X. G. and W.F. wrote the manuscript. XQ. L., X.G. and W.F. extracted and analyzed the data. XQ. L., X.G., X.W., W.F. and X.L. had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of data analysis. R.GM., J.J., Y.Z., Z.W. and Y.T. edited the manuscript.

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