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Research Paper

Fibrinogen as a Predictor of Depression and Cognitive Impairment After Ischemic Stroke: A Meta-analysis

Didan Ariadapa Rahadi[1*], Muhammad Irfan Pratama[2], Tegar Muhammad Abdillah[2]

1. Biomedical Master Program, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.
2. Department of Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

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Running Title Fibrinogen and PSD and PSCI After Ischemic Stroke

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ABSTRACT

Background: Acute ischemic stroke (AIS) is related to higher disability. Post-stroke depression (PSD) and post-stroke cognitive impairment (PSCI) are the two conditions, which significantly impact patient recovery and quality of life (QoL). Fibrinogen, an acute-phase protein, is elevated during AIS, and has been implicated in various neurological disorders.

Objectives: We assessed the association between higher fibrinogen levels and the risk of PSD and PSCI in AIS patients.

Materials & Methods: We conducted a meta-analysis of studies published up to June 2025 across three databases, including PubMed, ScienceDirect, and Web of Science. Eligible studies assessed the association between fibrinogen and PSD and PSCI among AIS patients.

Results: Our study included nine observational studies conducted in China, with a total sample size of 3.328 patients. The meta-analysis consistently demonstrated a significant positive association between elevated fibrinogen levels and an increased risk of both PSD and PSCI. For PSD, the adjusted odds ratio (aOR) across five studies was 1.43 (95% CI, 1.3%, 1.5%; P<0.00001). For PSCI, aOR from three studies was 1.59 (95% CI, 1.19%, 2.11%; P=0.002). These associations largely persisted after adjustment for various confounding factors. All included studies were conducted in China and predominantly involved male patients.

Conclusion: Elevated fibrinogen on admission was statistically positively correlated with an increased risk of PSD and PSCI incidence. Fibrinogen is a valuable prognostic biomarker for early stratification of patients with a high risk of developing neuropsychiatric complications after AIS.

Keywords: Fibrinogen, Ischemic stroke, Depression, Cognition

*** Corresponding Author:**
Didan Ariadapa Rahadi, MD.
Address: *Biomedical Master Program, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.*
Tel: *+62 (822) 43607986,* ***Fax:*** *+62 75132838*
E-mail: *didan.rohadi@gmail.com*

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Highlights

- Elevated fibrinogen levels predict a higher risk of PSD among AIS patients.
- Elevated fibrinogen levels predict a higher risk of PSCI among AIS patients.
- Fibrinogen may guide early neuropsychiatric risk stratification.

Introduction

Acute ischemic stroke (AIS) is related to higher mortality and disability worldwide [1]. In Southeast Asia, including Indonesia, AIS significantly contributes to national health burdens, with rising incidence and limited access to comprehensive neurorehabilitation services. Advances in reperfusion therapy have significantly improved survival rates for AIS patients. However, some stroke survivors may experience unfavorable post-stroke complications, such as post-stroke depression (PSD) and post-stroke cognitive impairment (PSCI) [2, 3]. These conditions profoundly impact quality of life (QoL), functional recovery, and long-term prognosis [4-6]. Understanding the pathogenesis and identifying early biomarkers for the condition is crucial for timely intervention and favorable outcomes.

Systemic inflammation and coagulation regulation contribute to the pathophysiology of stroke and subsequent complications [7]. Fibrinogen, an acute-phase protein and a main component of the coagulation cascade, is elevated during AIS, and has been implicated in various neurological disorders [8]. Several observational studies have reported associations between elevated fibrinogen levels and the increased risk of either PSD or PSCI [9, 10]. Nonetheless, findings have been inconsistent, and no prior meta-analysis has synthesized the evidence across both complications simultaneously. Understanding whether fibrinogen serves as a shared predictor for these neuropsychiatric outcomes may have significant clinical implications.

Therefore, our study aimed to assess the association between high fibrinogen levels and the increased risk of PSD and PSCI events among AIS patients.

Materials and Methods

Study design

We performed this systematic review and meta-analysis to assess the association between fibrinogen levels and PSD and PSCI among AIS patients. The methodology of this study adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [11].

Search strategy and study selection

We used three databases, including PubMed, Web of Science, and ScienceDirect, using specific keywords as follows: (Fibrinogen) AND (post-stroke depression) OR (depression) OR (post-stroke cognitive impairment) OR (cognitive impairment). Studies were included if they investigated the association between fibrinogen levels and PSD or PSCI in adult AIS patients. A key inclusion criterion was the reporting of adjusted odds ratios (aORs) with 95% confidence intervals (CI) for the association between fibrinogen and the outcomes. Studies were excluded if they did not provide multivariate analysis or aORs. Review articles, case reports, animal studies, and studies not focusing on ischemic stroke or the specified outcomes were also excluded.

Selection and data collection process

The electronic database was uploaded into the Rayyan AI website, and duplicates were automatically eliminated. DAR and MIP screened the titles and/or abstracts for relevance. DAR and MIP then assessed the full texts of potential articles using the inclusion criteria. The discussion between DAR and MIP resolved any disagreement consecutively. Articles from these criteria and relevant references cited in those articles were reviewed. The PRISMA flowchart is described in Figure 1.

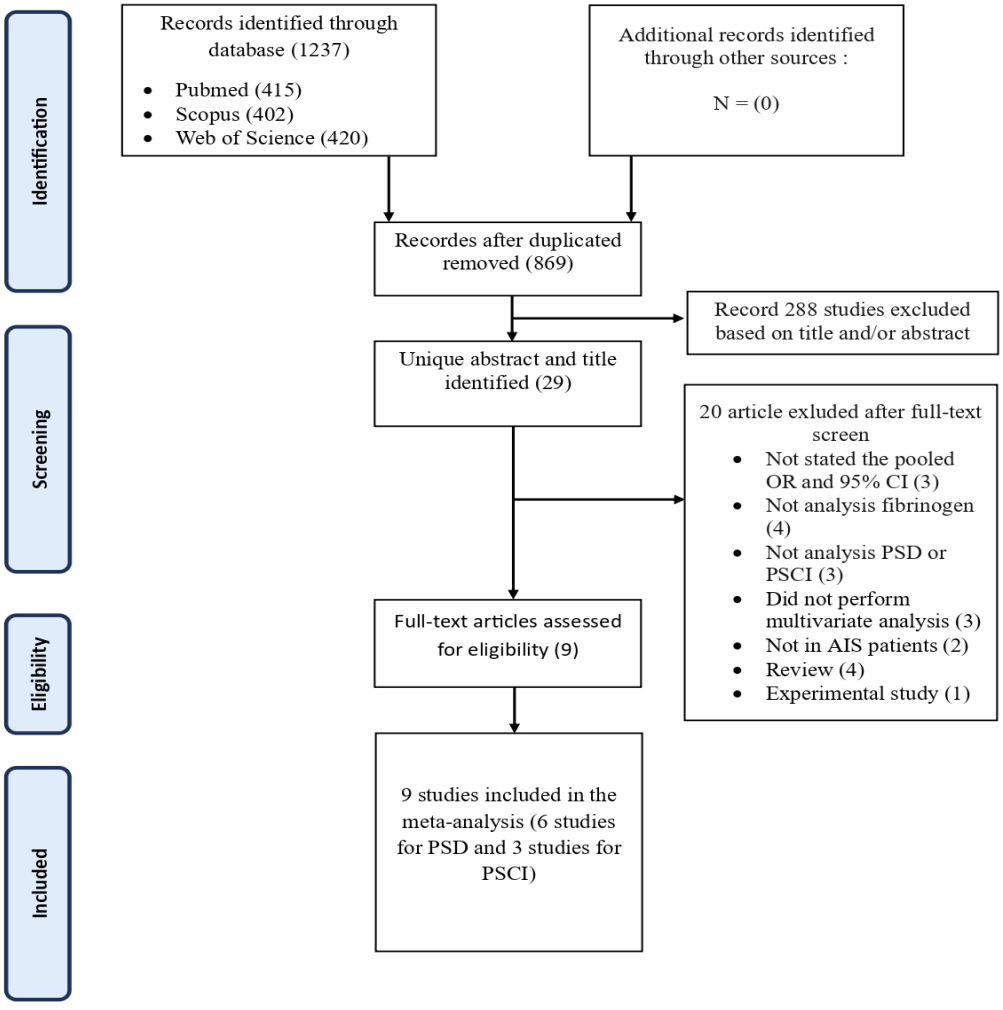

Figure 1. The PRISMA flow chart

PRISMA: The preferred reporting items for systematic reviews and meta-analyses.

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Data extraction

From each included study the following information were extracted: Name of author(s), year of publication, country, study design, number of samples, age, sex, time point of fibrinogen measurement, fibrinogen cut-off values, outcome, follow-up duration, the specific tools used for outcome assessment, and quality of study. Additionally, aORs with their 95% CIs for the association between fibrinogen and PSD or PSCI, along with the variables adjusted for in the multivariate analyses, were extracted.

Risk of bias assessment

A systematic methodology was performed to assess the quality and risk of bias for each included observational study. Study quality was evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies and the Newcastle-Ottawa scale (NOS) for cohort and case-control studies. The JBI scores were classified as low (0–4), moderate (5–6), and high (7–8). The NOS scores were classified as low (0–5) and high (6–9). The meta-analysis prioritized studies that provided multivariate (adjusted) analyses to mitigate confounding biases.

Statistical analysis

Excel and Review Manager 5.4 were used to analyze the data. For each outcome (PSD and PSCI), the aOR and its 95% CI were used to synthesize the findings across studies. A pooled estimate of the aOR was calculated using appropriate meta-analytic methods. Heterogeneity among studies was assessed, and a fixed or random-effect method was applied based on the level of heterogeneity. $P<0.05$ were considered significant.

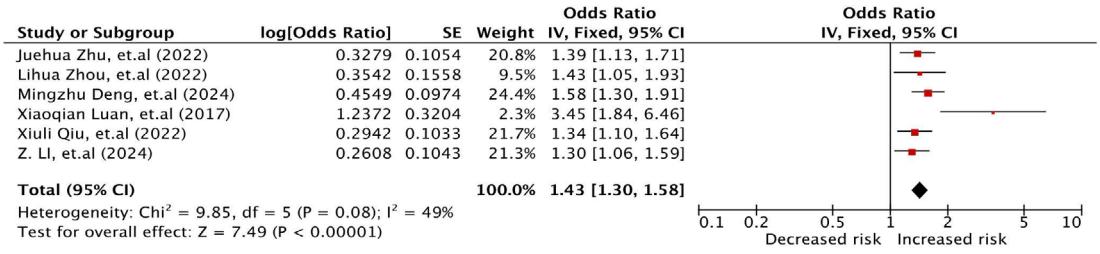

Figure 2. Forest plot showing the association between high fibrinogen and PSD

PSD: Post-stroke depression.

Results

Characteristic of the included studies

Nine observational studies with a total sample size of 3.328 patients were included. All studies were exclusively conducted in China, indicating a specific geographical focus; however, this suggests that the findings of this meta-analysis may have limitations in external generalizability. Study designs varied, comprising seven prospective cohort studies, one retrospective cohort, and one case-control study. Regarding patient demographics, the percentage of males often exceeded 60% in individual studies, and the mean or median age of participants generally ranged from adulthood to elderly. Fibrinogen levels were measured at various time points, including within 24 hours of admission, the morning after admission, 72 hours after the onset, or as soon as possible. PSD was assessed using the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) and the Hamilton depression rating scale 17-item (HAMD-17), while PSCI was evaluated using tools, such as the Montreal cognitive assessment (MoCA) and the mini-mental state examination (MMSE). Follow-up periods for outcomes also showed heterogeneity, ranging from 7 to 14 days after stroke to three months (Table 1).

Fibrinogen affects PSD in AIS

Six studies investigated the correlation between higher fibrinogen levels and PSD with five studies used both DSM-5 and HAMD-1, while one study used only HAMD-17 to assess PSD [12–17]. All studies consistently reported a positive and significant association. Higher fibrinogen levels were associated with a higher risk of PSD incident (aOR=1.43; 95% CI, 1.3%, 1.58%; P<0.00001) with moderate heterogeneity (I^2=49%) (Figure 2).

Fibrinogen affects cognitive impairment in AIS

Three studies investigated the association between fibrinogen levels and PSCI [9, 10, 18]. Among the included studies assessing PSCI, one study used MoCA, one study used MMSE, and one study used both tools. Similar to PSD, all three studies reported a positive and statistically significant association. Higher fibrinogen levels were associated with a higher risk of PSCI incident (aOR=1.59; 95% CI, 1.19%, 2.11%, P=0.002) with relatively low heterogeneity (I^2=46%) (Figure 3).

Publication bias analysis

All studies were of good quality, as indicated by the scores from the Newcastle-Ottawa quality assessment scales, and the details are summarized in Supplemental Table 1. The funnel plot appears asymmetrical in the distribution of studies around the vertical axis (Figure 4). This indicates the possibility of publication bias or a "small study effect" in this analysis. We did not perform a qualitative statistical analysis due to the small sample size.

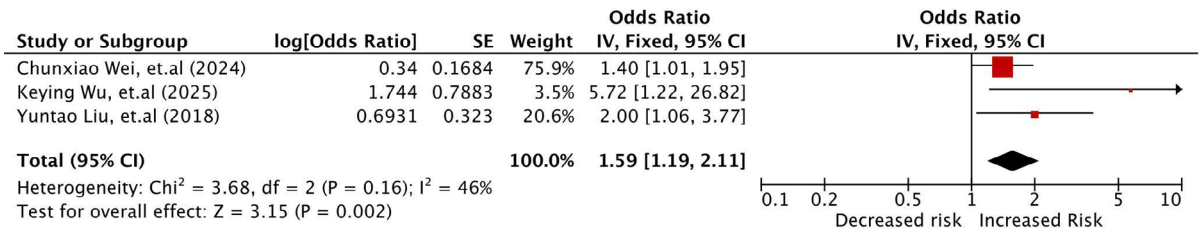

Figure 3. Forest plot showing the association betwee high fibrinogen and PSCI

PSCI: Post-stroke cognitive impairment.

Table 1. Characteristics of the included studies

Author(s), year	Country	Study Design	Number of Samples	Mean±SD/Median (IQR)	No (%)	Time to Measure Fibrinogen	Cut-off Value of Fibrinogen	Outcome	Follow-up	Measure(s)	Quality of Study
				Age (y)	Male						
Qiu et al. 2022 [12]	China	Prospective cohort	415	NR	415(78)	Within 24 h of admission	None	PSD	Three months	DSM-V criteria and HAMD-17	High
Zhu et al. 2022 [13]	China	Prospective cohort	PSD=95, Non-PSD=530, Total=625	PSD=65 (61–70), Non-PSD=65 (56–72), Total=65 (57–72)	PSD=48(50.5), Non-PSD=360(67.9), Total=406(64.9)	The morning after admission	≥3.08 g/L	PSD	Before discharge (day 7–14 after the onset of stroke)	HAMD-17	High
Zhou et al. 2022 [14]	China	Cohort retrospective	PSD=66, Non-PSD=280, Total=346	PSD=64 (59–68), Non-PSD=63 (53–70)	PSD=35(53), Non-PSD=189(67.5)	NR (baseline)	None	PSD	At 14±2 days after the onset of stroke	DSM-V criteria and HAMD-17	High
Deng et al. 2024 [15]	China	Prospective cohort	PSD=106, Non-PSD=274, Total=380	PSD=66.15±12 Non-PSD=64.42±11.22	PSD vs Non-PSD= 70(66.04) vs 211(77.01)	72 hours after the onset of stroke	≥2.95 g/L	PSD	Two weeks after stroke onset	DSM-V criteria and HAMD-17	High
Luan et al. 2017[16]	China	Prospective cohort	PSD=140, Non-PSD=266, Total=406	PSD=62.43±11.36 Non-PSD=62.52±10.02	PSD vs Non-PSD=81 vs 183	As soon as possible	≥3.69 g/L	PSD	One month after stroke	DSM-V criteria and HAMD-17	High
Li et al. 2024 [17]	China	Prospective cohort	PSD=90, Non-PSD=284, Total=374	PSD=63.63±10.18 Non-PSD=61.15±9.76	PSD vs Non-PSD=179(63.1) vs 42(46.6)	NR (baseline)	None	PSD	Three months	DSM-V criteria and HAMD-17	High
Wu et al. 2025 [18]	China	Case-control	PSCI=5, Non-PSCI=75, Total=150	PSCI=62.37 (8.56), Non-PSCI=62.17 (8.74), Total=62.27 (8.62)	PSCI=47(62.7), Non-PSCI=47(62.7), Total=94(62.7)	The next morning after hospital admission	>4 g/L	PSCI	NR	MoCA	High
Wei et al. 2024 [10]	China	Cohort prospective	PSCI=225, Non-PSCI=173, Total=398	PSCI=63 (58-69), Non-PSCI=60 (54-67)	PSCI=146(64.9), Non-PSCI=130(75.1)	Within 24 h of AIS onset	None	PSCI	7–14 days	MMSE and MoCA	High
Liu et al. 2018 [9]	China	Cohort prospective	PSCI=45, Non-PSCI=89, Total=134	PSCI=64.6±9.9, Non-PSCI=58.7±10.1	PSCI=19(42.2), Non-PSCI=70(78.6)	On admission	None	PSCI	Three months	MMSE, mRS, and BI	High

Abbreviations: HAMD-17: 17-item Hamilton depression rating scale; PSCI: Post-stroke cognitive impairment; PSD: Post-stroke depression; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; BI: Barthel index.

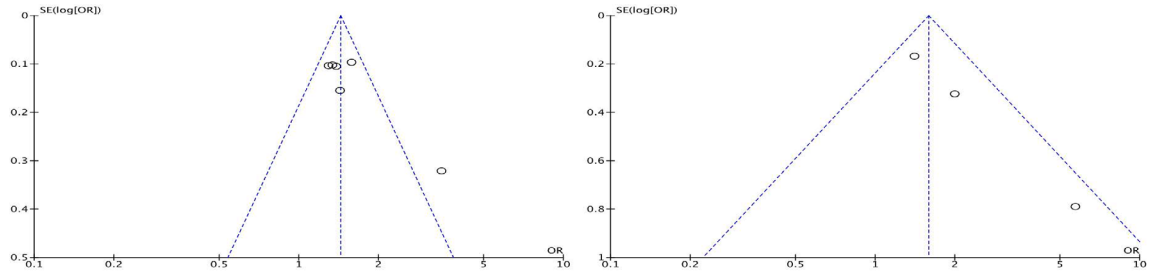

Figure 4. Forest plot showing the association betwee high fibrinogen and PSD (left) and PSCI (right)

PSD: Post-stroke depression; PSCI: Post-stroke cognitive impairment.

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Discussion

Interpretation and clinical implications of the findings

The results demonstrate a consistent correlation between higher fibrinogen levels and the risk of PSD and PSCI following an AIS event. Our findings suggest that fibrinogen may function not only as a marker of inflammation and coagulopathy but also as a potential prognostic biomarker for neuropsychiatric complications after ischemic stroke. Earlier studies have established a correlation between elevated fibrinogen levels and the risk of AIS [19, 20]. All included studies were conducted in China and involved predominantly male participants, which provides internal consistency but limits generalizability.

Mechanism

PSD is one consequence of this improved survival rate with approximately one in three stroke patients experiencing PSD [2, 21]. Stroke patients with PSD are associated with poor functional outcomes and QoL [4, 5]. Various mechanisms contribute to the occurrence of PSD, such as monoamine neurotransmitter imbalance, HPA axis dysfunction, glutamate-mediated neurotoxicity, neuroplasticity, and neuroinflammation [22]. During neuroinflammation, activated glial cells (microglia and astrocytes) are responsible for the synthesis and secretion of various pro-inflammatory mediators, such as cytokines, chemokines, and reactive oxygen species (ROS) [23]. A history of mental disorders is a major risk factor for PSD, along with other risk factors such as physical disability, female gender, elderly age, neuroticism, family history, stroke severity, and level of disability [24, 25]. High fibrinogen levels had a significantly positive association with depressive symptoms among hospitalized patients [26], those with spinal cord injury, the elderly undergoing video-assisted thoracoscopic surgery [27], and individuals with coronary heart disease [28, 29]. PSD risk factors other than fibrinogen include body mass index (BMI), hypertension, and diabetes as modifiable risk factors, while lesion location and age are considered non-modifiable risk factors [30].

PSCI is confirmed if a stroke patient shows a new onset of decreased cognitive function of any degree [31]. However, there is currently no consensus regarding the measurement of cognitive function in post-stroke patients [32]. More than 50% of patients may experience PSCI to varying degrees in the first year [3, 33]. The main risk factors for PSCI include age, neurodegeneration, and comorbidity [34]. PSCI is associated with a variety of poor clinical outcomes and contributes to reduced QoL. The pathophysiology of PSCI involves a complex interaction between acute vascular injury from the stroke and pre-existing brain vulnerabilities, such as small vessel disease and neurodegeneration, leading to neurovascular unit dysfunction and impaired brain connectivity [6]. High fibrinogen levels have been significantly associated with cognitive impairment among patients with chronic kidney disease [35], diabetic peripheral neuropathy [36], and after COVID-19 hospitalization [37].

Higher baseline fibrinogen levels reflect a combination of systemic inflammation and hypercoagulability, the main mechanisms of neuroinflammatory pathways. Fibrinogen can activate microglia and astrocytes, promoting the synthesis of increased levels of indoleamine-2,3-dioxygenase, which breaks down tryptophan into kynurenine [38, 39]. Tryptophan is a precursor of serotonin, while decreased tryptophan concentrations cause reduced synthesis of serotonin, a neurotransmitter involved in the pathophysiology of depression [39]. Fibrinogen-induced inflammatory cytokines also disrupt the blood-brain barrier and impair synaptic plasticity. [40]. These findings provide strong empirical support for the hypothesis that the acute-phase response and subsequent coagulation dysregulation reflected by elevated fibrinogen levels are not merely epiphenomena but an

actively involved mechanisms in mood disorders and cognitive deficits after AIS. Interestingly, the association between fibrinogen and PSD is sex-specific [12]. These mechanistic implications suggest that interventions targeting these pathways might have therapeutic potential.

Conclusion

Elevated fibrinogen levels are significantly associated with an increased risk of PSD and PSCI. These findings underscore the potential of fibrinogen as a valuable stratification biomarker for ischemic stroke, warranting further investigation into its mechanistic role and therapeutic implications. If validated in diverse populations, fibrinogen could be integrated into acute stroke risk stratification tools to facilitate early psychosocial intervention, neurocognitive screening, and personalized rehabilitation planning.

Study limitations and future research

Several limitations were identified in our study. First, all included studies were conducted in China, which may restrict the applicability of the results to other ethnic or geographic populations. Second, the timing of fibrinogen measurements varied across studies, potentially introducing heterogeneity. Third, although all studies adjusted for confounders, the specific variables included in the models differed, leading to possible residual confounding. Finally, the small number of studies precluded formal statistical testing for publication bias. Future research should aim to validate these findings in multiethnic cohorts, explore sex-specific effects, and investigate whether lowering fibrinogen levels could mitigate neuropsychiatric complications post-stroke. Moreover, the harmonization of assessment tools and time points across studies is essential to improve the comparability and interpretability of future meta-analyses.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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Authors contributions

Conceptualization, methodology, investigation, software, formal analysis, writing the original draft, and visualization: Didan Ariadapa Rahadi and Muhammad Irfan Pratama; Data curation, review, editing, and final approval: Didan Ariadapa Rahadi, Muhammad Irfan Pratama, and Tegar Muhammad Abdillah.

Conflict of interest

All authors declared no conflict of interest.

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Supplement Table 1. NOS critical appraisal of each study

No.	Study	Selection Items				Comparability Items		Outcome Items			Total
		Representativeness of exposed cohort	Representativeness of unexposed cohort	Ascertainment of exposure	Outcome not present at start of study	Age	NIHSS	Assessment of outcome	Follow-up length	Adequacy of follow-up	
1	Xiuli Qiu, et.al (2022)	★	★	★	★	★	★	★	★	★	7/9 (High)
2	Juehua Zhu, et.al (2022)	★	★	★	★	-	★	★	★	★	8/9 (High)
3	Lihua Zhou, et.al (2022)	★	★	★	★	-	★	★	★	★	8/9 (High)
4	Mingzhu Deng, et.al (2024)	★	★	★	★	★	★	★	★	★	9/9 (High)
5	Xiaoqian Luan, et.al (2017)	★	★	★	★	-	★	★	★	★	8/9 (High)
6	Z. LI, et.al (2024)	★	★	★	★	★	★	★	★	★	9/9 (High)
7	Keying Wu, et.al (2025)	★	★	★	★	-	-	★	★	★	7/9 (High)
8	Chunxiao Wei, et.al (2024)	★	★	★	★	★	★	★	★	★	9/9 (High)
9	Yuntao Liu, et.al (2018)	★	★	★	★	★	★	★	★	★	9/9 (High)