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The Association Between Serum Pentraxin-3 Level at Admission and the Functional Outcome of Patients After Acute Ischemic Stroke: A Meta-Analysis

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Background: Acute ischemic stroke (AIS) remains a leading cause of disability worldwide, placing a significant burden on patients' quality of life and healthcare systems. Pentraxin-3 (PTX-3), an inflammatory biomarker, may be associated with AIS prognosis; however, existing evidence is inconclusive.

Aims: To examine whether serum PTX-3 levels at admission are linked to the likelihood of poor functional outcomes in AIS patients.

Study Design: Systematic review and meta-analysis.

Methods: A comprehensive search of PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases was conducted to identify studies evaluating PTX-3 levels in AIS patients. Eligible studies included those that measured PTX-3 within 48 h of admission and evaluated outcomes using the modified Rankin Scale, with scores > 2 defined as poor outcomes. A random-effects model was used to calculate pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Results: Ten cohort studies involving1202 AIS patients were included. Higher PTX-3 levels at admission were significantly associated with an increased risk of poor functional outcomes (OR, 2.06; 95% CI, 1.72-2.47; $p < 0.001$), with no significant heterogeneity ($I^2 = 0\%$). Meta-regression showed that using higher PTX-3 cutoff values reported stronger associations ($p < 0.05$). Subgroup analyses confirmed consistent associations across study designs, patient characteristics, and timing of outcome assessment. The association was more pronounced in studies using a PTX-3 cutoff ≥ 3.3 ng/mL compared to those with a cutoff < 3.3 ng/mL.

Conclusion: Elevated serum PTX-3 levels at admission may serve as a prognostic biomarker for poor functional outcomes in AIS. Differences in PTX-3 cutoff values and potential residual confounding should also be considered. Further multicenter studies involving diverse populations are necessary to confirm these results and establish PTX-3 as a reliable prognostic indicator in clinical practice.

INTRODUCTION

Acute ischemic stroke (AIS) is a leading cause of death and long-term disability, affecting millions of people each year and imposing a substantial burden on healthcare systems worldwide.[1,2] Although treatments such as thrombolysis and thrombectomy have improved acute stroke care, many AIS patients still experience unfavorable outcomes, including physical and cognitive deficits.[3] Functional outcomes after AIS are typically assessed using the modified Rankin Scale (mRS), which ranges from 0 (no symptoms) to 6 (death).[4] A score > 2 on the mRS is commonly used to define poor functional outcomes, reflecting dependency in daily activities and reduced quality of life.[5] This level of disability not only affects patients directly but also places a significant burden on families and healthcare services, highlighting the importance of identifying reliable predictors of post-stroke outcomes to support timely treatment and rehabilitation planning.[6,7]

The prognosis of AIS is affected by various factors, including patient demographics, existing health conditions, and stroke severity.[8,9] Commonly recognized predictors of poor outcomes include age, stroke severity, comorbidities, and delays in treatment initiation.[10] However, these conventional factors do not fully explain the differences in patient outcomes, indicating the potential role of additional variables that may reflect biochemical changes and inflammation related to stroke.[11] Emerging biomarkers may enhance the ability to predict outcomes more accurately and support earlier,

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targeted interventions.[12] Pentraxin-3 (PTX-3), an inflammatory protein, has gained interest for its possible prognostic significance in AIS.[13,14] PTX-3 belongs to the PTX family and, although structurally different from C-reactive protein, is also involved in immune and inflammatory responses.[15] It is produced locally at inflammation sites by vascular cells and is believed to reflect both endothelial activation and tissue injury, making it a potential indicator of stroke outcomes.[16]

PTX-3 may have an important role in the development and progression of AIS by regulating inflammatory and immune responses that affect brain injury and recovery.[17] Its levels increase quickly following ischemic damage and inflammation, potentially worsening vascular and neuronal injury through its effects on the complement system, leukocyte activation, and degradation of the extracellular matrix.[18] These processes can lead to disruption of the blood-brain barrier (BBB), cerebral edema, and neuronal cell death, all of which may contribute to poorer functional outcomes.[19] Moreover, research has shown that PTX-3 levels are elevated in patients with more severe ischemic injury, indicating that PTX-3 may function not only as a marker of disease severity but also as a contributor to the progression of injury, potentially influencing both short- and long-term outcomes.[20]

Although PTX-3 has emerged as a potential prognostic biomarker in AIS, current studies examining its relationship with post-stroke functional outcomes have yielded inconsistent findings.[21-30] Variations in PTX-3 cutoff values and differences in the timing of measurement have contributed to these discrepancies. Some studies have reported that higher PTX-3 levels at admission are associated with worse outcomes.[21,22,26-28] while others have found no significant association.[23-25,29,30] In light of these conflicting results and the ongoing need for reliable prognostic indicators in AIS, a comprehensive evaluation of existing evidence is warranted. Therefore, we conducted a meta-analysis to assess the relationship between serum PTX-3 levels at admission and the risk of poor functional outcomes in patients with AIS.

MATERIALS AND METHODS

This study was conducted in accordance with the PRISMA 2020 guidelines[31] and the Cochrane Handbook for Systematic Reviews and Meta-Analyses[32], covering study design, data extraction, statistical analysis, and interpretation of findings. The study protocol was registered with PROSPERO under the registration number CRD42024613606.

Literature search

To identify relevant studies for this meta-analysis, we performed a comprehensive search of the PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and Wanfang databases. The search strategy used a combination of the following terms: 1) "pentraxin-3" OR "pentraxin 3" OR "PTX-3"; and 2) "stroke" OR "transient ischemic attack" OR "cerebral infarction" OR "cerebrovascular disorders." Only studies involving human subjects were included, and the search was limited to full-text articles published in English or Chinese in peer-reviewed journals. Detailed search strategies for each database are provided in Supplementary File 1. Additional relevant studies were identified by manually screening the reference lists of key original and review articles. The search covered all records from database inception up to October 12, 2024.

Inclusion and exclusion criteria

Inclusion criteria were established using the PICOS framework:

P (population): Adults (18 years or older) diagnosed with AIS, confirmed by clinical assessment and neuroimaging (computed tomography or magnetic resonance imaging), regardless of the treatment received.

I (exposure): Serum PTX-3 levels measured within 48 h of admission. Patients with elevated baseline PTX-3 levels were classified as the exposure group, based on the measurement methods and cutoff values reported in each original study.

C (comparison): Patients with lower PTX-3 levels at admission were considered as the comparison group.

O (outcome): The incidence of poor functional outcomes, defined as mRS score >2[33], was compared between high and low PTX-3 level groups. No restrictions were placed on follow-up duration, which typically ranged from hospital discharge to 3 months post-stroke.

S (study design): Both prospective and retrospective cohort studies were eligible.

Studies were excluded if they were reviews, editorials, meta-analyses, preclinical studies, or cross-sectional in design. Additional exclusion criteria included studies not focused on AIS patients, those lacking serum PTX-3 measurements as an exposure variable, or those that did not report functional outcomes during follow-up. When multiple studies used overlapping populations, only the study with the largest sample size was included in the meta-analysis.

Study quality assessment and data collection

Two authors independently performed the literature search, study selection, quality assessment, and data extraction. Any disagreements were resolved through discussion until consensus was achieved. The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS)[34], which rates studies on a scale of 1-9 based on selection of participants, control of confounding factors, and outcome assessment, with a score of 9 indicating the highest quality. The extracted data included the following: first author, year of publication, country, study design, patient characteristics (sample size, age, and sex), timing and methods used to measure serum PTX-3 levels, cutoff values used to define elevated PTX-3, duration of follow-up, number of AIS patients with poor functional outcomes, and the variables adjusted for in multivariate models evaluating the relationship between PTX-3 levels and stroke prognosis.

Statistical analysis

The relationship between serum PTX-3 levels and poor functional outcomes in AIS was evaluated using odds ratios (ORs) with 95%

confidence intervals (CIs), comparing patients with elevated PTX-3 levels at admission to those with lower levels. ORs and their standard errors were calculated from reported CIs or p values, followed by logarithmic transformation to stabilize variance. Heterogeneity among studies was assessed using the Cochrane Q test and the I^2 statistic,[35] with I^2 values above 50% indicating significant heterogeneity. A random-effects model was applied to account for differences in study populations and PTX-3 cutoff definitions.[32] Sensitivity analysis was conducted by sequentially removing individual studies to assess the robustness of the findings.[32] Univariate meta-regression was used to identify potential effect modifiers based on study characteristics, such as sample size, mean age, sex distribution, PTX-3 cutoff values, prevalence of poor outcomes, and NOS quality scores.[32] Predefined subgroup analyses were also carried out to assess the influence of study design, mean age, proportion of male participants, PTX-3 thresholds, follow-up periods, and study quality, using median values of continuous variables for subgroup classification. Publication bias was evaluated using funnel plots, visual inspection for asymmetry, and Egger's regression test.[36] All statistical analyses were performed using RevMan (Version 5.1, Cochrane Collaboration) and Stata (Version 17.0, Stata Corporation).

RESULTS

Study inclusion

The study selection process is summarized in Figure 1. The initial database search identified 453 records, from which 189 duplicates were removed. After screening titles and abstracts, 240 studies were excluded for not meeting the objectives of the meta-analysis. The full texts of the remaining 24 articles were independently reviewed by two authors, and 14 studies were excluded based on the predefined inclusion and exclusion criteria outlined in Figure 1. In total, 10 cohort studies met the eligibility criteria and were included in the final quantitative analysis.[21-30]

Overview of study characteristics

Table 1 provides a summary of the key characteristics of the studies included in the meta-analysis. In total, three prospective cohort studies[25,27,30] and seven retrospective cohort studies[21-24,26,28,29] were included, comprising 1202 AIS patients. These studies were published between 2015 and 2024 and all conducted in China. All studies focused on AIS patients, with participant ages ranging from 58.7 to 75.0 years and the proportion of male participants ranging from 45.9% to 75.5%. Serum PTX-3 levels were measured within 48 h of admission in all included studies. High serum PTX-3 level were defined using the different methods: the median value of PTX-3 in seven studies,[22,24-27,29,30] the third tertile of PTX-3 in one study,[23] and a cutoff derived from receiver operating characteristic curve analysis in another study.[28] The PTX-3 cutoff values for high levels ranged from 0.68 to 5.56 ng/mL. Functional outcomes were evaluated using the mRS at discharge in two studies,[26,30] at 1 month post-stroke in two studies,[21,22] and at 3 months post-stroke in six studies.[23-25,27-29] All studies used multivariate analysis to evaluate the association between admission PTX-3 levels and poor functional outcomes, adjusting for potential confounders such as age, sex, comorbidities, and baseline National Institutes of Health Stroke Scale scores. The NOS scores for these studies ranged from 6 to 9, indicating moderate to high study quality (Table 2).

Serum PTX-3 levels at admission and functional outcomes after stroke

A meta-analysis of 10 cohort studies[21-30] showed that higher serum PTX-3 levels at admission were significantly associated with a greater risk of poor functional outcomes after AIS (OR, 2.06; 95% CI, 1.72–2.47; $p < 0.001$; Figure 2a), with no significant heterogeneity (Cochrane Q test $p = 0.52$; $I^2 = 0\%$). Sensitivity analysis, performed by removing each study one at a time, confirmed these results (OR range, 1.92-2.20; $p < 0.05$ for all). Meta-regression analysis revealed a positive correlation between higher PTX-3 cutoff values and stronger associations with poor outcomes (coefficient = 0.17, $p = 0.04$; Table 3; Figure 2b). Other study factors, including sample size, mean age, male proportion, incidence of poor outcomes, and NOS scores, did not significantly impact the results ($p > 0.05$ for all; Table 3). Subgroup analyses showed no significant differences between retrospective and prospective studies ($p = 0.50$; Figure 3a), patients with mean ages < 63 years versus ≥ 63 years ($p = 0.39$; Figure 3b), or those with male proportions < 55% versus ≥ 55% ($p = 0.80$; Figure 4a). As suggested by meta-regression, a stronger association was found in studies with PTX-3 cutoff values ≥ 3.3 ng/mL compared to those with lower cutoffs (OR, 2.44 vs. 1.60; $p = 0.03$; Figure 4b). Further subgroup analyses revealed similar results across studies evaluating functional outcomes at 1 month or 3 months post-stroke ($p = 0.90$; Figure 5a) and between studies with NOS scores of 6-7 versus 8-9 ($p = 0.97$; Figure 5b).

Publication bias

Visual inspection of the funnel plots for the meta-analysis on serum PTX-3 levels and poor functional outcomes after AIS showed a symmetrical distribution, suggesting a low probability of publication bias (Figure 6). Additionally, Egger's regression test confirmed a minimal risk of publication bias ($p = 0.75$).

DISCUSSION

This meta-analysis reveals a significant association between elevated serum PTX-3 levels at admission and an increased risk of poor functional outcomes in AIS patients. Our findings suggest that PTX-3, an inflammatory biomarker associated with vascular and immune responses, may serve as a predictor of AIS prognosis. These results align with existing research, where higher PTX-3 levels have been linked to worse outcomes in various vascular conditions, supporting its potential as a prognostic marker for poor recovery in AIS. Subgroup and meta-regression analyses showed that studies using higher PTX-3 cutoffs were more likely to find a stronger association with poor outcomes, highlighting the need to standardize PTX-3 cutoff levels to improve predictive accuracy.

PTX-3 contributes to poor functional outcomes in AIS through several interconnected molecular mechanisms, including complement activation, inflammatory amplification, and endothelial

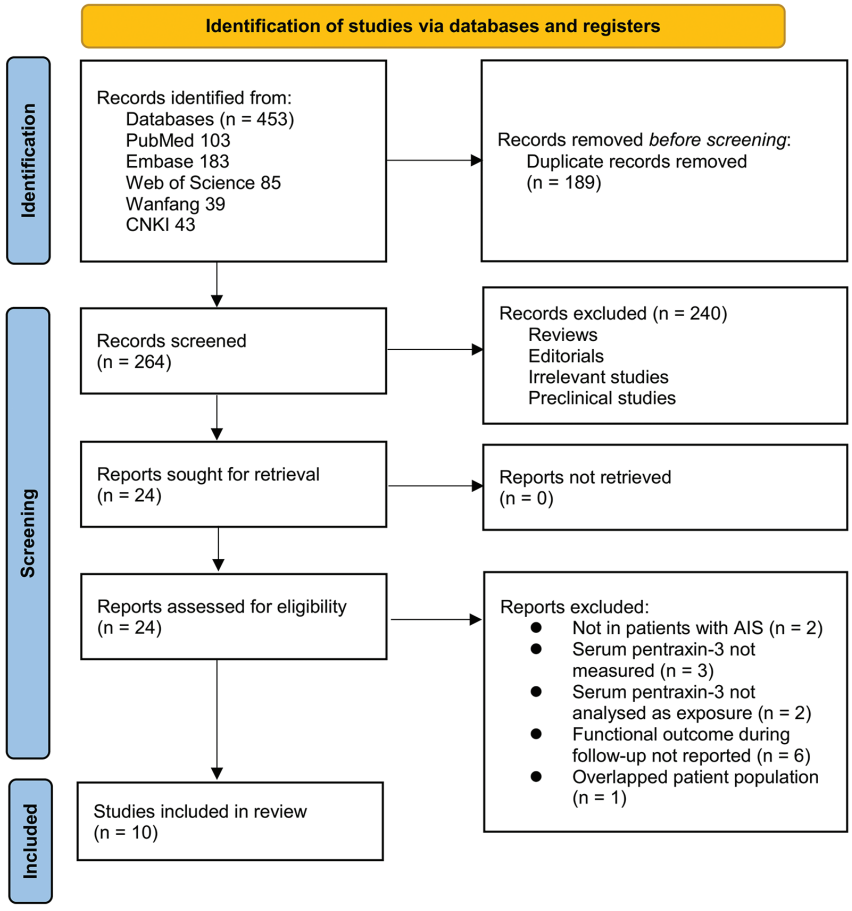

FIG. 1. Flowchart of the database search and study selection process.
CNKI, China National Knowledge Infrastructure.

dysfunction.[37] As an acute-phase protein, PTX-3 can enhance complement system activation by binding to C1q, triggering the classical complement cascade, which amplifies immune responses and leads to endothelial damage, BBB disruption, and neuronal apoptosis.[38,39] In addition to complement activation, PTX-3 may interact with pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6 (IL-6), and IL-1β, which play key roles in post-stroke inflammation.[13,40] By reinforcing cytokine signaling, PTX-3 can sustain inflammation, worsening ischemic injury and hindering neurovascular recovery.[41] Furthermore, PTX-3 may influence matrix metalloproteinase (MMP) activity, particularly MMP-9, which breaks down extracellular matrix components, causing BBB disruption, increased vascular permeability, and further neuroinflammation.[42] Additionally, PTX-3 is quickly produced by vascular endothelial cells after ischemia, where it interferes with nitric oxide signaling, disrupts cerebral autoregulation, and reduces microvascular perfusion, all of which contribute to secondary infarction and impaired neurological recovery.[43] Together, these mechanisms suggest that PTX-3 is not just a marker of inflammation but also actively contributes to ischemic injury, highlighting the need for future research on therapeutic interventions targeting PTX-3-related pathways to improve post-stroke outcomes.

Our subgroup and meta-regression analyses emphasize the importance of PTX-3 cutoff values in predicting functional outcomes after AIS. Studies using higher PTX-3 thresholds were more likely to report significant associations, suggesting that elevated levels are necessary to accurately reflect clinically significant inflammation and endothelial damage. Nevertheless, the association between PTX-3 levels and outcomes remained consistent across other subgroup analyses, suggesting that PTX-3's role in poor functional outcomes is likely robust across different patient profiles. These consistent results reinforce the potential of PTX-3 as a reliable biomarker for adverse outcomes in AIS. Our analysis also considered multivariate studies, confirming that the association between PTX-3 levels and functional outcomes is independent of established prognostic factors such as age and baseline stroke severity.

This meta-analysis has several strengths, including the inclusion of cohort studies that provide a longitudinal view of PTX-3 levels and functional outcomes, as well as multivariate adjustments in most studies to control for confounding factors. These study designs improve the reliability of our findings, as the cohort data establish a temporal link between PTX-3 levels at admission and subsequent functional outcomes. The consistency of the results across studies further supports the value of PTX-3 as a predictive biomarker.

TABLE 1. Characteristics of the Included Cohort Studies.

Study	Location	Study design	No. of patients with AIS	Mean age (years)	Men (%)	Timing of PTX-3 measurement	Methods of PTX-3 measurement	Methods for determining the PTX-3 cutoff	Cut-off of PTX-3 (ng/mL)	Follow-up duration (months)	No. of patients with poor functional outcome	Variables adjusted
Zhang and Qi[22]	China	RC	112	66.2	56.3	Within 24 h after admission	ELISA	Median	5.56	1	60	Age, sex, hsCRP, TC/HDL-C, WBC, FBG, and NIHSS at admission
Lin et al.[21]	China	RC	98	75	45.9	Within 24 h after admission	ELISA	NR	6	1	45	Age and sex
Zhang et al.[23]	China	RC	47	63.3	63.8	At admission	ELISA	T3	0.68	3	NR	Age, sex, comorbidities, and NIHSS at admission
Qu et al.[24]	China	RC	90	NR	63.3	At admission	ELISA	Median	2.98	3	57	Age, sex, comorbidities, FBG, and time from disease onset to thrombolysis
Zhang et al.[25]	China	PC	241	60.8	75.5	Within 48 h after admission	ELISA	Median	3.13	3	31	Age, sex, comorbidities, NIHSS at admission, and stenosis of ICA > 50%
Pan et al.[26]	China	RC	139	NR	NR	At admission	ELISA	Median	2	At discharge	35	Age and sex
Liu et al.[28]	China	RC	195	60.4	47.2	At admission	ELISA	ROC curve analysis derived	3.31	3	54	Age, sex, comorbidities, NIHSS at admission, and time from disease onset to thrombolysis
Jiang et al.[12]	China	RC	92	61.2	48.9	Within 24 h after admission	ELISA	Median	1.42	3	23	Age, sex, NIHSS at admission, and size of the infarction
Ao et al.[27]	China	PC	82	58.7	57.3	At admission	ELISA	Median	4.11	3	21	Age, sex, comorbidities, NIHSS score at admission, and time from disease onset to intervention
Liu et al.[28]	China	PC	106	63.1	54.7	Within 24 h after admission	ELISA	Median	5.19	At discharge	26	Age, sex, AF, NIHSS at admission

RC, retrospective cohort; PC, prospective cohort; AIS, acute ischemic stroke; PTX-3, pentraxin-3; NR, not reported; ELISA, enzyme-linked immunosorbent assay; NIHSS, National Institute of Health Stroke Scale; ICA, intracranial artery; T3, the third tertile; ROC, receiver operator characteristics; hsCRP, high-sensitivity C-reactive protein; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; FBG, fasting blood glucose; AF, atrial fibrillation.

TABLE 2. Study Quality Evaluation Using the Newcastle-Ottawa Scale.

Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of the exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of the outcome	Enough long follow-up duration	Adequacy of follow-up of the cohort	Total
Zhang and Qi[22]	0	1	1	1	1	1	1	0	1	7
Lin et al.[21]	0	1	1	1	1	0	1	0	1	6
Zhang et al.[23]	1	1	1	1	1	1	1	1	1	9
Qu et al.[24]	0	1	1	1	1	1	1	1	1	8
Zhang et al.[25]	1	1	1	1	1	1	1	1	1	9
Pan et al.[26]	0	1	1	1	1	0	1	1	0	6
Liu et al.[28]	0	1	1	1	1	1	1	1	1	8
Jiang et al.[12]	0	1	1	1	1	1	1	1	1	8
Ao et al.[27]	1	1	1	1	1	1	1	1	1	9
Liu et al.[28]	1	1	1	1	1	1	1	1	1	9

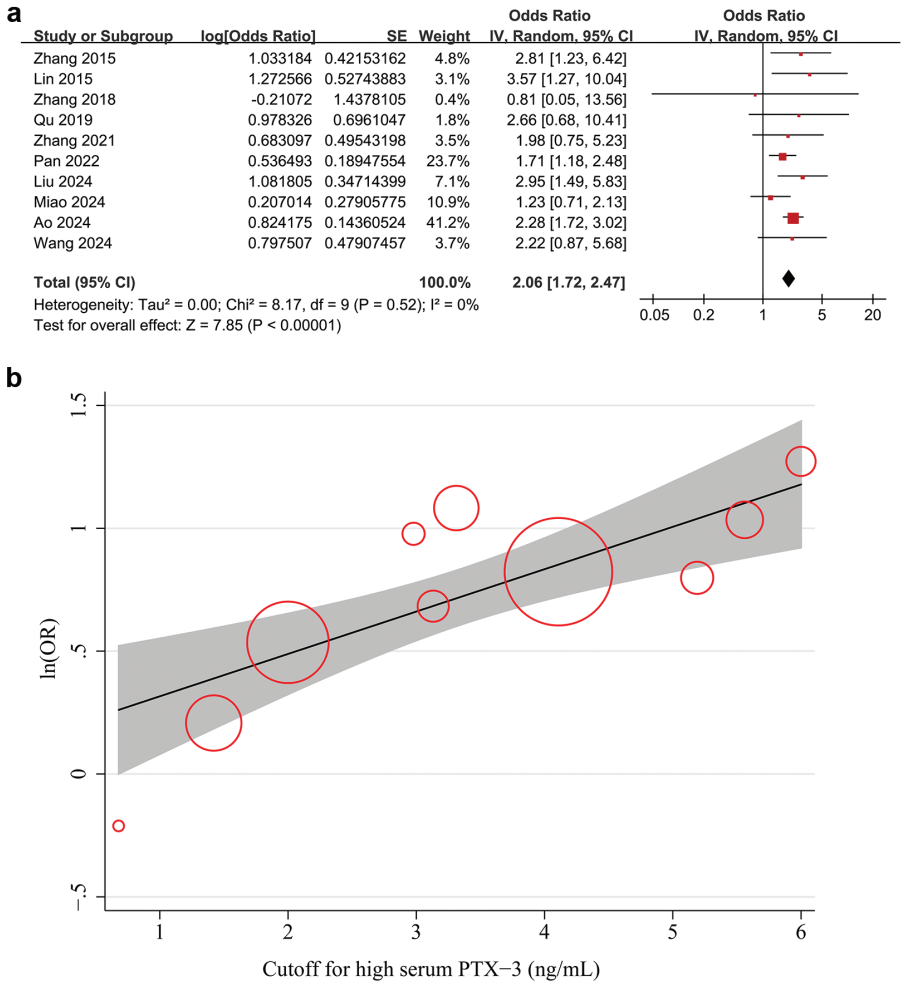

FIG. 2. Forest plots for the meta-analysis on the relationship between serum PTX-3 levels at admission and poor functional outcomes after AIS. a, forest plots for the overall meta-analysis; b, plots showing the correlation between PTX-3 cutoffs and the natural logarithm of the OR (LnOR), illustrating the association between PTX-3 levels and poor functional outcome after AIS.

PTX-3, pentraxin-3; AIS, acute ischemic stroke; OR, odds ratio.

TABLE 3. Results of the Univariate Meta-Regression Analysis.

	OR for the association between circulating PTX-3 and functional outcomes after AIS		
Variables	**Coefficient**	**95% CI**	***p* values**
Sample size	0.00091	-0.00525-0.00708	0.74
Mean age (years)	0.016	-0.059-0.091	0.64
Men (%)	0.0069	-0.0309-0.0446	0.69
Cutoff value of PTX-3 (ng/mL)	0.17	0.01-0.33	0.04
Incidence of poor functional outcome (%)	0.012	-0.013-0.037	0.30
NOS	0.024	-0.199-0.248	0.81

PTX-3, pentraxin-3; AIS, acute ischemic stroke; OR, odds ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale; 3.1 [JP].

However, there are limitations that should be considered when interpreting these findings. One major limitation is that all included studies were conducted in China, which may limit the generalizability of our results to other populations. Differences in genetic factors, lifestyle, and environmental influences could affect PTX-3 levels and its role in stroke pathophysiology. Additionally, variations in healthcare systems and stroke management practices across regions could influence the prognostic value of PTX-3 in different populations. The lack of ethnic diversity in the study population limits our ability to determine whether PTX-3 has the same predictive value across different racial and ethnic groups. Future research including multiethnic cohorts from various regions is needed to confirm these findings and explore the influence of genetic and environmental factors on the relationship between PTX-3 and stroke outcomes. Standardizing PTX-3 measurement methods and cutoff values across diverse populations will be essential for broader clinical applicability. Additionally, the variability in PTX-3 cutoff values across studies may introduce heterogeneity, though

our meta-regression analysis showed that higher PTX-3 thresholds were associated with stronger links to poor outcomes. Standardizing PTX-3 measurements and defining clinically relevant cutoff values would enhance its role as a prognostic biomarker. Furthermore, as with all meta-analyses of observational studies, there may be residual confounding factors. While most studies adjusted for important variables like age, stroke severity, and comorbidities, unmeasured factors, such as differences in stroke management protocols and rehabilitation, could have influenced the observed associations. The retrospective design of several studies also presents a risk of selection bias.[44] Lastly, this meta-analysis focused on PTX-3 levels at admission, and we could not assess changes in PTX-3 levels over time. Longitudinal studies tracking PTX-3 levels during both the acute and recovery phases of AIS would provide valuable information about its role in stroke progression and recovery.

From a clinical standpoint, these findings suggest that measuring PTX-3 levels at admission could provide valuable prognostic information for AIS patients, helping to identify those at high risk for poor functional recovery. PTX-3 measurements could complement traditional prognostic factors, such as age and baseline severity scores, to develop a more comprehensive risk profile for individual patients. This approach could facilitate targeted interventions to reduce inflammation and vascular damage early in treatment. However, due to the lack of standardized PTX-3 cutoff values, further research is needed to establish clinically meaningful thresholds for risk stratification and treatment planning. Future studies should focus on validating these findings in diverse populations and exploring potential therapeutic strategies targeting PTX-3 pathways. Randomized controlled trials investigating anti-inflammatory agents that modify PTX-3 or its downstream effects in AIS could provide insights into whether PTX-3 is just a marker or an active participant in the pathological process. Additionally, longitudinal studies with repeated PTX-3 measurements could clarify how PTX-3 levels change during the recovery period and whether these changes are linked to long-term outcomes. Understanding these patterns could enhance our ability to use PTX-3 as a real-time indicator of recovery potential. Moreover, given the strong association between elevated

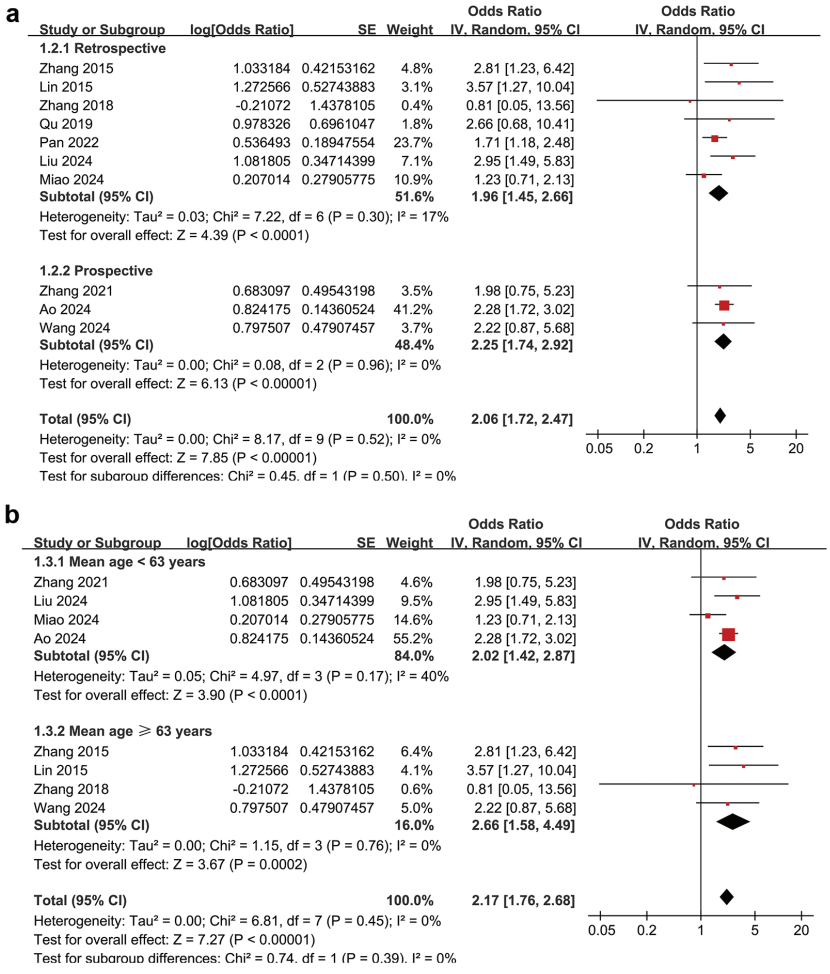

FIG. 3. Forest plots for subgroup analyses of the association between serum PTX-3 levels at admission and poor functional outcomes after AIS. a, subgroup analysis based on study design; b, subgroup analysis based on the mean age of the patients.

PTX-3, pentraxin-3; AIS, acute ischemic stroke; CI, confidence intervals.

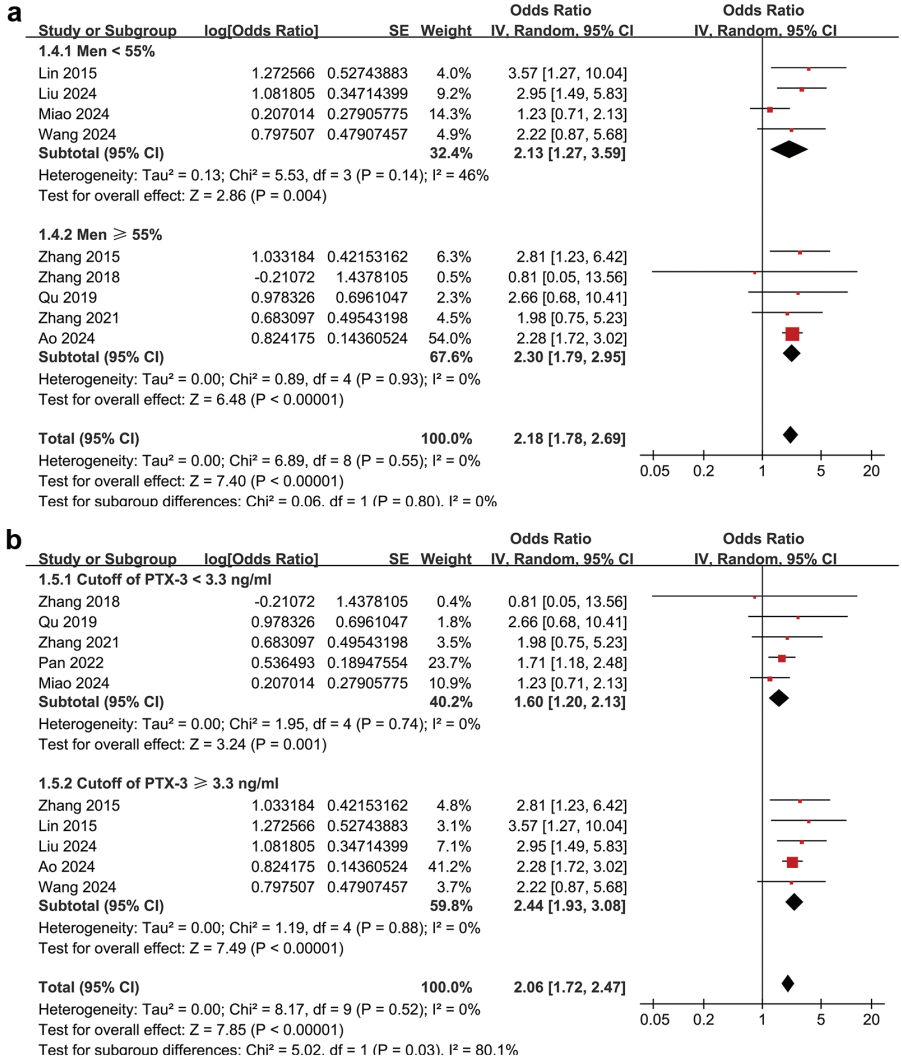

FIG. 4. Forest plots for subgroup analyses of the association between serum PTX-3 levels at admission and poor functional outcomes after AIS. a, subgroup analysis based on the proportion of male participants; b, subgroup analysis based on the cutoff value for defining high PTX-3 levels.
PTX-3, pentraxin-3; AIS, acute ischemic stroke; CI, confidence intervals.

PTX-3 levels and poor functional outcomes in AIS, therapeutic strategies aimed at modifying PTX-3 pathways may offer potential for improving stroke recovery. One approach could focus on targeting PTX-3-mediated complement activation, as excessive complement cascade activation has been linked to secondary ischemic injury.[45] Inhibitors of complement components, such as C1q blockers or complement pathway inhibitors, may help reduce PTX-3-driven neuroinflammation and endothelial dysfunction.[46] Additionally, anti-inflammatory agents that suppress PTX-3 production, such as corticosteroids or IL-6 inhibitors, could reduce its harmful effects on BBB integrity and neuronal survival.[47] Another potential strategy is regulating MMP activity, especially MMP-9, which is influenced by PTX-3 and contributes to BBB breakdown. MMP inhibitors, such as minocycline or other neuroprotective agents, could lessen PTX-3-induced vascular damage and enhance neurological recovery.[48] Although these approaches are still mainly investigational, future research should investigate whether pharmacological modulation of PTX-3 or its downstream pathways can provide clinical benefits for AIS patients.

In conclusion, this meta-analysis confirms that elevated serum PTX-3 levels at admission are associated with a higher risk of poor functional outcomes in AIS patients. PTX-3 shows potential as a prognostic biomarker due to its involvement in inflammatory and endothelial injury pathways, which may worsen ischemic damage and hinder recovery. While the consistency of our findings across multiple subgroups strengthens the results, limitations related to study design and generalizability highlight the need for further validation. Standardizing PTX-3 cutoff values and examining its role in AIS pathophysiology through targeted therapies may improve its clinical utility in predicting and potentially enhancing outcomes in AIS.

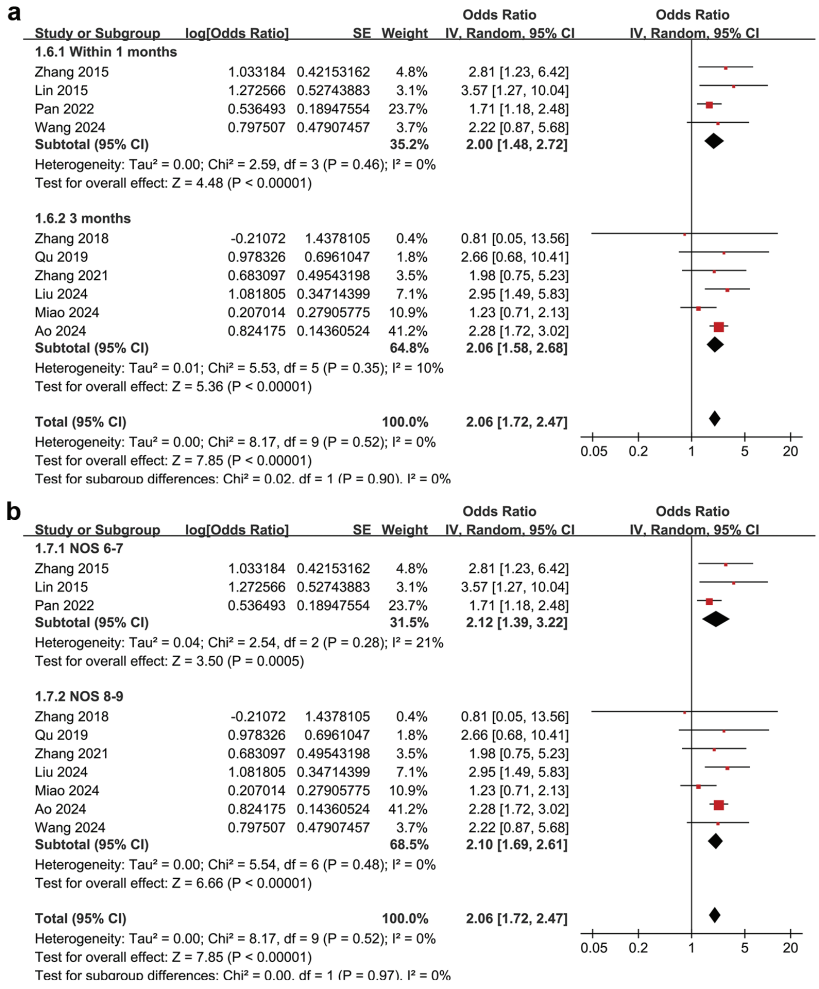

FIG. 5. Forest plots for the subgroup analyses of the relationship between serum PTX-3 levels at admission and poor functional outcomes after AIS. a, subgroup analysis based on follow-up duration; b, subgroup analysis based on NOS scores.

PTX-3, pentraxin-3; AIS, acute ischemic stroke, NOS, Newcastle–Ottawa Scale; CI, confidence intervals.

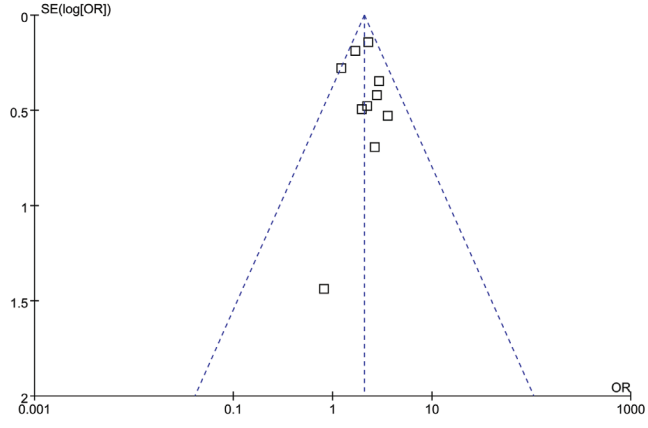

FIG. 6. Funnel plots for meta-analyses of the associations between serum PTX-3 levels at admission and poor functional outcomes after AIS.

PTX-3, pentraxin-3; AIS, acute ischemic stroke; OR, odds ratio.

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- Y.Z., K.H.; Design- Y.Z., K.H.; Data Collection or Processing- Y.Z., F.K., X.Z., K.H.; Analysis or Interpretation- Y.Z., F.K., X.Z., K.H.; Literature Search- Y.Z., F.K., X.Z., K.H.; Writing-Y.Z.; Critical Review- Literature Search- Y.Z., F.K., X.Z., K.H.

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Supplementary Table 1: https://balkanmedicaljournal.org/img/files/36-SUPPLEMENTARY-TABLE%201.pdf

REFERENCES

1. Thayabaranathan T, Kim J, Cadilhac DA, et al. Global stroke statistics 2022. *Int J Stroke.* 2022;17:946-956. [CrossRef]
2. Martin SS, Aday AW, Almarzooq ZI, et al. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation.* 2024;149):e347-e913. [CrossRef]
3. Saceleanu VM, Toader C, Ples H, et al. Integrative approaches in acute ischemic stroke: from symptom recognition to future innovations. *Biomedicines.* 2023;11:2617. [CrossRef]
4. Chye A, Hackett ML, Hankey GJ, et al. Repeated measures of modified rankin scale scores to assess functional recovery from stroke: AFFINITY study findings. *J Am Heart Assoc*. 2022;11:e025425. [CrossRef]
5. Saver JL, Chaisinanunkul N, Campbell BCV, et al. Standardized nomenclature for modified rankin scale global disability outcomes: consensus recommendations from stroke therapy academic industry roundtable XI. *Stroke.* 2021;52:3054-3062. [CrossRef]
6. Alawieh A, Zhao J, Feng W. Factors affecting post-stroke motor recovery: implications on neurotherapy after brain injury. *Behav Brain Res.* 2018;340:94-101. [CrossRef]
7. Stinear CM, Lang CE, Zeiler S, Byblow WD. Advances and challenges in stroke rehabilitation. *Lancet Neurol.* 2020;19:348-360. [CrossRef]
8. Torres-Aguila NP, Carrera C, Muiño E, et al. Clinical variables and genetic risk factors associated with the acute outcome of ischemic stroke: a systematic review. *J Stroke.* [CrossRef]
9. Abujaber AA, Albalkhi I, Imam Y, et al. Predicting 90-day prognosis in ischemic stroke patients post thrombolysis using machine learning. *J Pers Med.* 2023;13:1155. [CrossRef]
10. Winstein CJ, Stein J, Arena R, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke.* 2016;47:98-169. [CrossRef]
11. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke.* 2021;52:e364-e467. [CrossRef]
12. Jiang F, Li J, Yu S, Miao J, Wang W, Xi X. Body fluids biomarkers associated with prognosis of acute ischemic stroke: progress and prospects. *Future Sci OA.* 2024;10:FSO931. [CrossRef]
13. Fornai F, Carrizzo A, Forte M, et al. The inflammatory protein Pentraxin 3 in cardiovascular disease. *Immunity Ageing.* 2016;13:25. http://doi.org/10.1186/s12979-016-0080-1
14. Ristagno G, Fumagalli F, Bottazzi B, et al. Pentraxin 3 in Cardiovascular Disease. *Front Immunol.* 2019;10:823. [CrossRef]
15. Inoue K, Kodama T, Daida H. Pentraxin 3: a novel biomarker for inflammatory cardiovascular disease. *Int J Vasc Med.* 2012;2012:657025. [CrossRef]
16. Ramirez GA, Rovere-Querini P, Blasi M, et al. PTX3 Intercepts Vascular Inflammation in Systemic Immune-Mediated Diseases. *Front Immunol.* 2019;10:1135. [CrossRef]
17. Rodriguez-Grande B, Swana M, Nguyen L, et al. The acute-phase protein PTX3 is an essential mediator of glial scar formation and resolution of brain edema after ischemic injury. *J Cereb Blood Flow Metab*. 2014;34:480-488. [CrossRef]
18. Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: friend and foe for ischemic stroke. *J Neuroinflammation.* 2019;16:142. [CrossRef]
19. de Oliveira THC, Souza DG, Teixeira MM, Amaral FA. Tissue Dependent Role of PTX3 During Ischemia-Reperfusion Injury. *Front Immunol.* 2019;10:1461. [CrossRef]
20. Kouchaki E, Babamohammadi A, Nikoueinejad H, Sehat M. Association of serum levels of pentraxin-3, m-ficolin, and surfactant protein a with the severity of ischemic stroke. *Iran J Allergy Asthma Immunol.* 2017;16:140-146. [CrossRef]
21. Lin Q, He YL, Fu XH, Huang L. The correlation between plasma pentraxin-3 and the severity and short-term prognosis of acute ischemic stroke patients. *Chin J Gerontol.* 2015;35:6781-6783. [CrossRef]
22. Zhang B, Qi LQ. Correlation between plasma pentraxin-3 and severity and recent prognosis in elderly patients with acute ischemic stroke. *Chin J Neuroimmunol Neurol.* 2015;22:57-61. [CrossRef]
23. Zhang CY, Han HD, Wang SY, Huang SR, Deng BQ. Pentraxin-3 in thrombolytic therapy for acute ischemic stroke: no relation with curative effect and prognosis. *Med Sci Monit*. 2018;24:4427-4432. [CrossRef]
24. Qu LX, Li GQ, Fei R, Fu ZP, Chen YX, Liu DB. Clinical value of serum pentraxin 3 and caveolin- 1 in evaluating the prognosis of thrombolytic therapy for patients with acute ischemic stroke. *Chin J Arterioscler.* 2019;27(9):774-778. [CrossRef]
25. Zhang Y, Hu H, Liu C, Wu J, Zhou S, Zhao T. Serum pentraxin 3 as a biomarker for prognosis of acute minor stroke due to large artery atherosclerosis. *Brain Behav.* 2021;11:e01956. [CrossRef]
26. Pan AL, Fang WJ, Hong L, Yang S. Changes of serum sCD40L, PTX3, and GFAP in patients with acute ischemic stroke and their role in evaluating the condition and prognosis. *Med Pharm J Chin PLA.* 2022;34:111-114. [CrossRef]
27. Ao P, H. K, Gao C, Liu F. Changes in the levels of pentraxin 3, matrix metalloproteinase-9, and omentin-1 before and after intervention in acute ischemic stroke and their combined predictive value for prognosis. *Cardio-Cerebrovasc Dis Prev Treat*. 2024;24:59-63. [CrossRef]
28. Liu GF, Wang WW, Wang JX, Yuan Y, Xu CX, Han S. The predictive value of thromboelastography parameters combined with serum PTX3 and sTLT-1 for poor prognosis in patients with acute ischemic stroke. *Lab Med Clin.* 2024;9(21):2557-2563. [CrossRef]
29. Ruirui M, Aixia S, Panpan L. The relationship between peripheral blood PTX3, osteopontin levels and neurological function, infarct size, and prognosis in patients with acute ischemic stroke. *J Clin Exp Med*. 2024;23(2):137-141. [CrossRef]
30. Yibing W, Lei Z, Jianjun C, Cheng C, Guozhi S. Correlation analysis of serum irisin, pentraxin-3, chemokine like factor 1 and poor prognosis in patients with acute ischemic stroke after vascular intervention treatment. *Chin J Med.* 2024;59:1124-1126. [CrossRef]
31. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. [CrossRef]
32. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. The Cochrane Collaboration. 2021. [CrossRef]
33. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol.* 2006;5:603-612. [CrossRef]
34. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2010. [CrossRef]
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539-1558. [CrossRef]
36. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634. [CrossRef]
37. Zhang H, Wang R, Wang Z, et al. Molecular insight into pentraxin-3: update advances in innate immunity, inflammation, tissue remodeling, diseases, and drug role. *Biomed Pharmacother.* 2022;156:113783. [CrossRef]
38. Lu J, Teh B, Wang L, et al. The classical and regulatory functions of c1q in immunity and autoimmunity. *Cell Mol Immunol.* 2008;5:9-21. [CrossRef]
39. Liu H, Jiang M, Chen Z, et al. The Role of the complement system in synaptic pruning after stroke. *Aging Dis.* 2024. [CrossRef]
40. Zhu H, Hu S, Li Y, et al. Interleukins and Ischemic Stroke. *Front Immunol.* 2022;13:828447. [CrossRef]
41. Doni A, Garlanda C, Mantovani A. PTX3 orchestrates tissue repair. *Oncotarget.* 2015;6:30435-30436. [CrossRef]
42. Tian W, Kyriakides TR. Matrix metalloproteinase-9 deficiency leads to prolonged foreign body response in the brain associated with increased IL-1beta levels and leakage of the blood-brain barrier. *Matrix Biol.* 2009;28:148-159. [CrossRef]
43. Carrizzo A, Lenzi P, Procaccini C, et al. Pentraxin 3 induces vascular endothelial dysfunction through a p-selectin/matrix metalloproteinase-1 pathway. *Circulation*. 2015;131:1495-1505 [CrossRef]
44. Barría M. Limitations and biases in cohort studies. In: Barría RM, editor. *Cohort Studies in Health Sciences.* IntechOpen; 2018:Ch. 3. [CrossRef]
45. Garred P, Tenner AJ, Mollnes TE. Therapeutic targeting of the complement system: from rare diseases to pandemics. *Pharmacol Rev.* 2021;73:792-827. [CrossRef]

46. Orsini F, De Blasio D, Zangari R, Zanier ER, De Simoni MG. Versatility of the complement system in neuroinflammation, neurodegeneration and brain homeostasis. *Front Cell Neurosci*. 2014;8:380. [CrossRef]
47. Mallick R, Basak S, Chowdhury P, et al. Targeting cytokine-mediated inflammation in brain disorders: developing new treatment strategies. *Pharmaceuticals (Basel)*. 2025;18:104. [CrossRef]
48. Zhang H, Chang M, Hansen CN, Basso DM, Noble-Haeusslein LJ. Role of matrix metalloproteinases and therapeutic benefits of their inhibition in spinal cord injury. *Neurotherapeutics*. 2011;8:206-220. [CrossRef]