Magna Neurologica Vol. 4, No. 2, July 2026

https://journal.uns.ac.id/magna-neurologica
DOI: 10.20961/magnaneurologica.v4i2.3308
e-ISSN 2985-3729 p-ISSN 2963-6027

REVIEW ARTICLE **OPEN ACCESS**

BLOOD-BASED BIOMARKERS FOR PREDICTING POST-STROKE PROGNOSIS: A SCOPING REVIEW OF PENTRAXIN-3, NEUROPENTRAXIN-1, AND NEUROPENTRAXIN-2

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Article History:
Received: February 13, 2026
Accepted: May 21, 2026
Published: July 15, 2026

Cite this as:
Divina E, Ghozali SAS, Prawiroharjo P. Blood-Based Biomarkers for Predicting Post-Stroke Prognosis: A Scoping Review of Pentraxin-3, Neuropentraxin-1, and Neuropentraxin-2. Magna Neurologica 4(2) July 2026: 175-186. 10.20961/magnaneurologica.v4i2.3308

ABSTRACT

Background: Stroke remains a major global health challenge, with substantial losses in disability-adjusted life-years, particularly in low-middle-income countries. Predicting post-stroke outcomes remains challenging because outcomes are driven by complex and overlapping processes, including inflammation, vascular injury, and neurodegeneration. Consequently, blood-based biomarkers, such as the pentraxin group that reflect underlying pathophysiology, have gained attention. However, existing evidence is fragmented and heterogeneous, underscoring the need for systematic mapping of the pentraxin group as biologically informed prognostic tools.
Objective: This systematic scoping review aims to map and synthesize existing evidence on the prognostic value of blood-based biomarkers Pentraxin-3 (PTX3), Neuropentraxin-1 (NPTX1), and Neuropentraxin-2 (NPTX2) in predicting clinical outcomes after stroke.
Methods: This PRISMA-ScR–guided scoping review systematically mapped evidence on blood-based biomarkers: PTX3, NPTX1, and NPTX2, for post-stroke prognosis from 6 databases and used NOS for quality assessment.
Results: A total of 18 studies were included in the final scoping review. Lower serum NPTX2 levels were significantly associated with post-stroke cognitive impairment. Studies investigating PTX3 demonstrated substantial heterogeneity in sampling timing, cutoff definitions, and follow-up duration. Across studies, higher PTX3 concentrations were independently associated with increased mortality (AUC ~0.73–0.81, P value <0.0001), greater baseline neurological severity as measured by the National Institutes of Health Stroke Scale (NIHSS), and poorer functional outcomes assessed by the modified Rankin Scale (mRS).
Conclusion: Despite the large heterogeneity of studies, the overall evidence supports PTX3, NPTX1, and NPTX2 as less-invasive prognostic blood-based biomarkers for post-stroke outcomes. However, studies on NPTX1 and NPTX2 are still very limited.

Keywords: blood-based biomarker, neuropentraxin 1, neuropentraxin 2, pentraxin 3, stroke

Introduction

Stroke, whether ischemic or hemorrhagic, remains one of the leading causes of death and disability worldwide, with recent estimates of nearly 12 million per year, including millions of deaths and tens of millions of disability-adjusted life-years (DALYs) lost annually. Particularly concentrated in low- and middle-income regions where health systems struggle to cope, stroke remains one of the top causes of global neurologic disability and death across age groups.[1,2] Predicting individual post-stroke outcomes is a challenge due to the stroke pathophysiological processes, including immune and inflammatory cascades within the brain and systemic circulation, contributing to blood–brain barrier disruption, leukocyte infiltration, and secondary neuronal damage. These responses profoundly influence recovery and long-term deficits.[3]

Blood-based biomarkers reflecting stroke pathophysiology are being actively investigated to improve prognostic accuracy. Among these, pentraxin-3 (PTX3), an acute-phase protein associated with vascular and tissue inflammation, has shown consistent associations with poorer functional outcomes and higher mortality across multiple stroke cohorts and meta-analyses, in some cases outperforming conventional markers such as C-reactive protein.[4,5] Neuropentraxin-1 (NPTX1) and neuropentraxin-2 (NPTX2), members of the same Pentraxin family linked to synaptic plasticity and neurodegenerative processes, may offer complementary prognostic insights, although current evidence is largely derived from animal models.[6,7] Overall, the literature remains heterogeneous in study design, timing of biomarker assessment, populations, and outcomes, and no single circulating biomarker has been widely adopted in clinical practice, underscoring the need for systematic mapping of evidence to clarify biomarker utility, identify knowledge gaps, and inform development of integrated, biologically grounded prognostic tools for stroke care.

There is an explicit knowledge gap regarding the use of neuronal pentraxins in human stroke studies, as current evidence for NPTX1 and NPTX2 is largely derived from animal models or theoretical proteomic experiments. Clinical data remains extremely limited, with the current literature identifying only one human cohort study that specifically evaluates the prognostic value of NPTX2 in post-stroke patients. Hence, a scoping review approach was selected rather than a meta-analysis because the existing evidence is still highly fragmented, with a large heterogeneity in study methods. A scoping review enables researchers to systematically map the available evidence while accommodating methodological heterogeneity across studies. This systematic scoping review aims to map and synthesize existing evidence on the prognostic value of blood-based biomarkers NPTX1 and NPTX2 in predicting clinical outcomes after stroke.

Methods

Study Design

The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) and followed the methodological framework proposed by Arksey and O'Malley, as further refined by the Joanna Briggs Institute (JBI). This review has been registered to Open Science Framework with registration DOI number: 10.17605/OSF.IO/SWZU3. These frameworks guided the identification, selection, and synthesis of relevant literature.

Research Question (PCC Framework)

The research question of this literature utilizes the Population Concept Context (PCC) framework, as follows:

1. Population: Patients with stroke
2. Concept: Prognostic use of blood-based biomarkers Pentraxin 3, Neuropentraxin 1, and Neuropentraxin 2
3. Context: All clinical and healthcare settings

Literature Search Strategy

A comprehensive literature search was conducted across electronic databases, including PubMed/MEDLINE, Scopus, ProQuest, ClinicalKey, Cochrane, and individual searches. Keywords and search dates on each database is presented in the attachment.

Eligibility Criteria

Inclusion Criteria

Studies were eligible for inclusion if they met the following criteria:

1. Human studies of any observational (e.g., cohort, case–control, cross-sectional) or interventional design
2. Studies evaluating blood-based PTX3, NPTX1, or NPTX2 in patients with stroke
3. Studies reporting post-stroke clinical outcomes, including but not limited to mortality, functional disability, or recovery

Exclusion Criteria

Studies were excluded if they were:

1. Editorials, commentaries, letters
2. Case reports/small case series (if excluded)
3. Animal or in-vitro studies

Study Selection Process

All retrieved records were imported into a reference management software, and duplicate records were removed. Two reviewers (ED and SASG) independently screened titles and abstracts to assess eligibility based on the predefined inclusion and exclusion criteria. Studies deemed potentially relevant were then subjected to full-text review. Discrepancies at any stage of the screening process were resolved through discussion and consensus. The study selection process was documented using a PRISMA flow diagram, detailing the number of records identified, screened, excluded, and included in the final review.

Data Charting and Synthesis

Data from included studies were extracted using a standardized data charting form. Extracted information included publication year, geographic region, study design, stroke subtype, biomarker assessed, timing of blood sampling, and reported prognostic outcomes. The results were synthesized descriptively to map the extent, nature, and characteristics of the available evidence.

Results

Study Selection Results

The database search yielded a total of 182 records. After duplicate records were removed, 137 unique studies remained for title and abstract screening. Full-text articles were retrieved and assessed for eligibility (28 studies). Following full-text review, 109 studies were excluded for reasons including [e.g., wrong population, irrelevant outcomes, non-human studies, or insufficient data]. Ultimately, 18 studies met the inclusion criteria and were included in the final scoping review. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

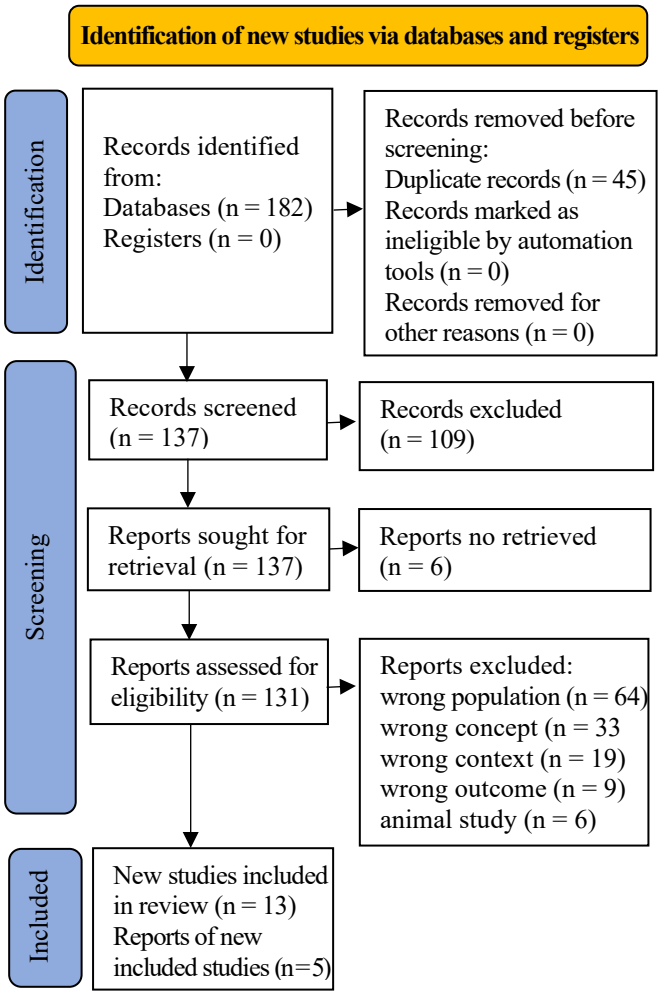

Figure 1. PRISMA Chart

Findings in Pentraxin-3

We found 15 studies on serum blood-based PTX3 and post-stroke outcomes. Ten were prospective studies with varied follow-up periods between discharge and up to about six years, 3 were reviews, 1 was a cross-sectional study, and 1 was a meta-analysis study. Twelve studies centered on ischemic stroke, two were centered on cerebral hemorrhage, while one encompassed all types of strokes. Across a total of 2,741 patients with cerebrovascular disease, most studies were conducted in China over the past decade and predominantly involved male patients (Table 1).

Table 2 summarizes 11 clinical studies (non-review and non-meta-analysis), evaluating PTX3 as a prognostic biomarker in post-stroke patients across different stroke subtypes, sampling times, and outcome measures. Overall, most studies report significantly elevated PTX3 levels in stroke patients than in controls, particularly in acute ischemic stroke, intracerebral hemorrhage, and acute cerebral infarction, with measurement commonly obtained within the first 12–72 hours after admission Elevated PTX3 concentrations were consistently associated with greater stroke severity, poorer functional outcomes, and increased mortality. Several studies also demonstrated moderate-to-good prognostic performance for predicting adverse outcomes, using ROC analysis (AUC ~0.73–0.81).

In ischemic stroke, higher PTX3 levels were consistently linked to worse prognosis. Studies have shown that elevated PTX3 correlated with vascular risk factors, infarct burden, stroke severity, and higher mortality rates, particularly in the highest PTX3 tertiles.[9,10,19] Patients with PTX3 concentrations ≥ 6.02 ng/mL also demonstrated significantly higher NIHSS scores compared with those with lower levels.[16] However, not all findings were uniform; some studies reported no significant association between early PTX3 levels and poor prognostic outcomes, including neurological outcomes.[17,18,4]

In hemorrhagic stroke, PTX3 also showed prognostic relevance. Higher PTX3 levels were significantly associated with increased mortality in intracerebral hemorrhage, with high sensitivity and specificity for predicting survival.[13] Additionally, a stepwise increase in PTX3 concentrations with increasing stroke severity has been demonstrated, supporting its role as an inflammatory marker reflecting neurological damage.[15] Collectively, these findings suggest that PTX3 is a promising biomarker reflecting inflammation and disease severity after stroke, although its independent prognostic value may vary depending on stroke subtype, timing of measurement, and outcome assessed. Notably, outcomes in one study were limited to early neurological deterioration, with other prognostic endpoints not specified.[9] We also considered studies included in a previous meta-analysis; however, of the nine studies included, six could not be retrieved due to a lack of international publication, and one was a duplicate from our search.[5] Moreover, after reviewing a related systematic review, it was excluded because it pooled PTX3 measurements from multiple biological samples (blood, cerebrospinal fluid, saliva, and urine), precluding extraction of blood-specific PTX3 data.[21]

Table 1. The Characteristics of Studies on Pentraxtins-3 as Prognostic Biomarker for Post-Stroke

Author Year (References)	Country	Study Design	Type of stroke	Number of patients (n)	Mean age (years ± SD)	Men (%)	Time of PTX3 taken	Method of detection[8]	No of patients with poor prognosis	Follow up period
Peng 2025[8]	China	Review	Ischemic stroke	N/A	N/A	N/A	N/A	N/A[9]	N/A	N/A
Cao 2025[9]	China	Prospective cohort	Acute ischemic stroke	289	66	69.6	72h of admission	ELISA[5]	82*	At discharge
Zhu 2025[5]	China	Meta Analysis	Acute ischemic stroke	1,202	63	58.2	24h-48h of admission	ELISA[10]	352	At discharge - 3 months
Hervella 2024[10]	Spain	Prospective Case-Control	Acute Ischemic Lacunar Stroke	120	66.5	68.3	48h of admission	ELISA[11]	35	3 months
Lv 2023[11]	China	Review	Intracerebral Hemorrhage	N/A	N/A	N/A	N/A	N/A[12]	N/A	N/A
Zhang 2022[12]	China	Review	All types	N/A	N/A	N/A	N/A	N/A[13]	N/A	N/A
Hao 2021[13]	China	Prospective cohort	Intracerebral hemorrhage	175	67.22	60	24h of admission	ELISA[14]	69	At discharge
Lambert 2020[14]	Norway	Prospective cohort	Ischemic stroke or TIA	17	69.2	25	7 days of onset	ELISA[15]	9	At discharge
Kouchaki 2017[15]	Iran	Cross-Sectional Study	Ischemic stroke	82	70.2	51.2	24h-96h of onset	ELISA[16]	18	At discharge
Qin 2016[16]	China	Prospective cohort	Acute cerebral infarction	96	65.18	67.8	At admission	ELISA[17]	42	1 month
Ceylan 2014[17]	Turkey	Prospective cohort	Acute ischemic stroke	44	72.4	40.9	12h of admission	ELISA[18]	N/A	7 days
Sezer 2014[18]	Turkey	Prospective cohort	Acute ischemic stroke	52	68.2	67.7	24h of admission	ELISA[19]	41	3 months
Ryu 2012[19]	South Korea	Prospective cohort	Acute ischemic stroke	376	63.6	66	24h of admission	ELISA[4]	73	1-2246 days
Zhang 2021[4]	China	Prospective cohort	Acute minor ischemic stroke	241	61.27	74.7	48h of admission	ELISA[20]	31	3 months
Zhang CY 2018[20]	China	Prospective cohort	Acute ischemic stroke	47	63.3	63.8	At admission	ELISA	25*	3 months

*patients with neurological deficit and/or without neurological improvement

Table 2. Comparison of Studies on Pentraxtins-3 as Prognostic Biomarker for Post-Stroke Patients

Author Year (References)	Type of stroke	No. of patients (n)	Time of PTX3 taken	No of patients with poor prognosis	Follow up period	Methods of determining cutoff	Cutoff (ng/mL)	Other outcomes
Cao 2025[9]	Acute ischemic stroke	289	72h of admission	82	At discharge	ROC AUC 0.742 (95 % CI = 0.680–0.804, p < 0.001	16.23	1. PTX3 correlated significantly with diastolic blood pressure, Ox-LDL, and plaque burden on admission.
Hervella 2024[10]	Acute Ischemic Lacunar Stroke	120	48h of admission	35	3 months	Mean P value <0.0001	2188.5	1. Serum level of PTX3 was significantly elevated in patients with deep lacunar infarcts compared to the other group (2528.5±1495.7 versus 1660.5±1140.1pg/mL) 2. Concentrations of PTX3 were significantly elevated in patients with poor outcomes compared to those with good outcomes (3334.8±1659.5 versus 2202.8±1304.7pg/mL, p=0.003)
Hao 2021[13]	Intracerebral hemorrhage	175	24h of admission	69	At discharge	ROC analysis AUC of PTX3 in predicting alive and deceased patients is 0.801 (p<0.001)	9.997	1. PTX3 is significantly higher in deceased stroke patients (19.34 (95% CI 2.95-30.97), p<0.001) 2. PTX3 sensitivity and specificity to predict survived vs deceased are 0.927 and 0.932
Lambert 2020[14]	Ischemic stroke or TIA	17	7 days of onset	9	At discharge	ROC analysis	0.0092	1. PTX3 can predict AF from patients with cryptogenic stroke (AUC>0.90, p<0.05). AF leads to the most mortality in CS.
Kouchaki 2017[15]	Ischemic stroke	82	24h-96h of onset	18	At discharge	Mean serum level	Mild stroke severity 0.00453 Moderate stroke severity 0.00818 Severe stroke severity 0.01098	1. The more severe the stroke was, the higher levels of serum level of PTX3, M-ficolin, and SPA (p<0.001) 2. Significant correlation between PTX3 (0.723), Mficolin (0.736), and SPA (0.731) with stroke severity according to mNIHSS score (p<0.001) 3. Every unit increase in the level of mNIHSS increased the serum level of PTX3 as 0.47, M-ficolin as 0.08 and SPA as 4.9 units in regression model.

Table 2. Comparison of Studies on Pentraxtins-3 as Prognostic Biomarker for Post-Stroke Patients

Author Year (References)	Type of stroke	No. of patients (n)	Time of PTX3 taken	No of patients with poor prognosis	Follow up period	Methods of determining cutoff	Cutoff (ng/mL)	Other outcomes
Qin 2016[16]	Acute cerebral infarction (ACI)	96	At admission	42	1 month	Median	High concentration: PTX3 ≥ 6.02 Low concentration: PTX3 < 6.02	1. PTX3 levels in ACI patients were significantly higher than those in healthy controls [(6.02 ± 1.87) μg/L vs. (1.51±0.21) μg/L, t = 2.956, p = 0.004 < 0.05]. 2. NIHSS scores and mRS scores were significantly higher in patients of high concentration group (6.87 ± 0.93) than the low concentration group (4.26 ± 0.88) (p < 0.05)
Ceylan 2014[17]	Acute ischemic stroke	44	12h of admission	N/A	7 days	Median	1st day of stroke: 0.05 (0.01-1610) 7th day of stroke: 0.04 (0.01-0.86)	1. Multivariate analysis demonstrated that serum PTX3 levels measured on day 1 or day 7 after stroke were not associated with the final NIHSS score. 2. Patients were stratified into three subgroups based on their baseline NIHSS scores, and no significant differences were observed in either initial or follow-up PTX3 concentrations across the groups.
Sezer 2014[18]	Acute ischemic stroke	52	24h of admission	41	3 months	Median (Tertile 1-3 limits)	1st tertile: 3.49 2nd tertile: 7.02 3rd tertile: 16.38	1. Median serum PTX3 levels were higher in stroke patients than in control subjects, with statistically significant differences (P = 0.037). 2. There were no differences in NIHSS, MRS, comorbidity, and infarct volume among all three tertiles of PTX3 statistically.
Ryu 2012[19]	Acute ischemic stroke	376	24h of admission	73	1-2246 days	Median (Tertile 1-3 limits)	1st tertile: < 4.9 2nd tertile: 4.9–11.8 3rd tertile: > 11.8	1. The overall mortality rate of the first, second, and third tertiles were 7.2%, 11.9%, and 39.2%. 2. The hazard ratio of the second and third tertiles of PTX3 were 1.82 (95% CI, 0.80–4.15), and 6.40 (3.14–13.02), p<0.001

Table 2. Comparison of Studies on Pentraxtins-3 as Prognostic Biomaker for Post-Stroke Patients

Author Year (References)	Type of stroke	No. of patients (n)	Time of PTX3 taken	No of patients with poor prognosis	Follow up period	Methods of determining cutoff	Cutoff (ng/mL)	Other outcomes
Zhang 2021[4]	Acute minor ischemic stroke	241	48h of admission	31	3 months	Mean	3.14	1. AUC for PTX3 at the 95% CI for the ROC analysis was 0.726 (0.598–0.855) 2. No statistically significant differences were obtained between PTX3 in predicting an unfavorable outcome
Zhang CY 2018[20]	Acute ischemic stroke	47	At admission	25	3 months	Median (Tertile 1-3 limits)	1st tertile: <0.555 2nd tertile: 0.555-0.687 3rd tertile: >0.687	1. No significant difference was found in initial and 24 hour PTX3 levels between patients with neurological improvement and without neurological improvement (p=0.72 and p=0.36, respectively). 2. There were significant differences between patients with neurological improvement and without neurological improvement in the treatment within 3 hours (p=0.03) and the 24 hours for NIHSS score (P<0.001). 3. Initial and 24 hour PTX3 levels had no association with 24 hour neurological improvement. Based on the multivariable analysis by logistic regression, no difference between PTX3 levels and the neurological improvement was found (p>0.05).

Table 3. The Characteristics of Studies on Neuropentraxins as Prognostic Biomarker for Post-Stroke Patients

Author Year (References)	Country	Study Design	Type of stroke	Number of patients (n)	Mean age (years ± SD)[22]	Men (%)	Biomarkers
Li 2025[22]	China	Cohort study	Acute ischemic stroke	134	66.99 ± 11.777	70.1	NPTX2
San Jose 2022[7]	Germany	Review	All type	N/A	N/A23	N/A	NPTX1, NPTX2
Chapman 2020[23]	Canada	Review	All type	N/A	N/A	N/A	NPTX2

Table 4. Quality Assessment of Included Studies Using Newcastle-Ottawa Scale[24]

	Sample Selection					Comparability		Outcome		
Author Year (References)	**Clearnes of aim**	**Sample representativeness**	**Sample size**	**Non-respondents**	**Exposure assessment**	**Control of other confounding factors**	**Comparability of participants**	**Assessment of the outcome**	**Statistical test**	**NOS Total Score (Quality Assessment) (0-16)**
Peng 2025[8]	2	0	0	0	0	0	0	0	0	2
Cao 2025[9]	2	1	2	2	1	1	1	2	2	14
Zhu 2025[5]	2	1	2	2	1	1	1	2	2	14
Hervella 2024[10]	2	1	2	2	1	1	1	2	2	14
Lv 2023[11]	2	0	0	0	0	0	0	0	0	2
Zhang 2022[12]	2	1	2	2	1	1	1	2	2	14
Hao 2021[13]	2	1	2	2	1	1	1	2	2	14
Lambert 2020[14]	2	1	1	1	1	0	1	2	2	11
Kouchaki 2017[15]	2	1	2	2	1	1	1	2	2	14
Qin 2016[16]	2	1	2	2	1	1	1	2	2	14
Ceylan 2014[17]	2	1	1	1	1	1	1	2	2	12
Sezer 2014[18]	2	1	2	2	1	0	1	2	2	13
Ryu 2012[19]	2	1	2	2	1	1	1	2	2	14
Zhang 2021[4]	2	0	0	0	0	0	0	0	0	2
Zhang CY 2018[20]	2	1	2	1	1	1	1	2	1	12
Li 2025[22]	2	1	2	2	1	1	1	2	2	14
San Jose 2022[7]	2	0	0	0	0	0	0	0	0	2
Chapman 2020[23]	2	0	0	0	0	0	0	0	0	2

Findings in Neuropentraxins

We found only one cohort study that investigated NPTX2 as a prognostic predictor for post-stroke cognitive impairment in patients with acute ischemic stroke (Table 3). The study was conducted in China with 134 patients and found that serum NPTX2 levels were significantly lower in patients with post-stroke cognitive impairment (PSCI) ($p < 0.05$).[22] Multivariate logistic regression analysis, using the NPTX2 cut-off value (0.986 ng/mL) as a binary categorical variable, showed that lower NPTX2 levels (<0.986 ng/mL) remained an independent risk factor for PSCI (odds ratio [OR] = 0.075, 95% CI 0.010–0.812, $p < 0.01$).[22] The other two studies on neuropentraxins were review articles encompassing current non-human and theoretical evidence on the use of NPTX proteins as post-stroke prognostic indicators, which are discussed in the discussion section.

Study Quality Assessment

We used a modified Newcastle–Ottawa Scale for systematic reviews to assess the studies included. The modified scale ranged from 0 to 16 points, with higher scores indicating better methodological quality. Studies scoring <9 were considered low quality, 9–12 moderate quality, and 13–16 high quality (Table 4).[24]

Discussion

Pentraxin–3 as Indicator for Post-Stroke Prognosis

Pentraxin-3 is a 42-kDa long pentraxin acute-phase, 381 amino acid glycoprotein comprising a unique N-terminal domain and a conserved C-terminal pentraxin domain, assembling mainly as asymmetric disulfide-linked octamers. This structure enables PTX3 to bind diverse ligands, including growth factors, extracellular matrix components, complement proteins, and microbial structures, supporting roles in angiogenesis inhibition, matrix organization, and innate immune regulation. PTX3 also carries a variably diallylated N-glycosylation site in the C-terminal domain, with cell- and stimulus-dependent glycosylation patterns that further modulate ligand binding and immune function.[12] It is produced locally at sites of inflammation by endothelial cells, macrophages, dendritic cells, and vascular smooth muscle cells, distinguishing it from liver-derived short pentraxins such as C-reactive protein.[25] Notably, in the acute phase of stroke, PTX3 can be produced by reactive astrocytes located in the peri-infarct area.[26]

PTX3 is rapidly upregulated following ischemia, tissue injury, and vascular inflammation and plays a central role in innate immunity, complement activation, and endothelial regulation.[27] In cerebrovascular disease, elevated circulating PTX3 levels have been consistently associated with greater stroke severity, larger infarct volume, and poorer clinical outcomes.[4,5] Mechanistically, PTX3 reflects inflammatory activation driving blood–brain barrier disruption, endothelial dysfunction, and secondary neuronal injury, central to post-stroke pathophysiology.[5,27] Clinically, accumulating evidence supports PTX3 as a prognostic biomarker for stroke, particularly in relation to mortality and functional disability. In a retrospective study involving patients with aneurysmal subarachnoid hemorrhage admitted within 24 hours of onset, higher cerebrospinal fluid PTX3 levels were significantly associated with poor 3-month outcomes.[29] Multiple observational studies and meta-analyses have demonstrated that higher plasma PTX3 levels in the acute phase of ischemic stroke are independently associated with poorer functional outcomes and increased short- and long-term mortality.[4,5]

Other studies further reported that PTX3 outperforms traditional inflammatory markers in prognostic assessment.[28,30] Now, growing evidence indicates that elevated PTX3 has been linked to post-stroke complications, especially on unfavorable neurological recovery, underscoring its utility as a marker of systemic and vascular inflammatory burden.[4,18,19] These findings position PTX3 as one of the most well-validated blood-based biomarkers for post-stroke prognosis, capturing inflammation-driven vascular and neuronal injury processes that critically influence long-term disability and survival.[4,5] However, Ceylan et al.[17] concluded the contrary, that PTX3 does not correlate significantly with post-stroke prognostic outcomes. Despite that, most studies report a favorable association between PTX3 levels and prognostic outcomes.

Neuronal Pentraxinx as Indicators for Post-Stroke Prognosis

Neuropentraxin-1 and Neuropentraxin-2 are 47-kDa secreted long pentraxins involved in synaptic function, with NPTX1 linked to neurodegeneration and cognitive decline and NPTX2 regulating excitatory synapse formation and plasticity.[7] Animal and proteomic studies indicate that NPTX1 is enriched at excitatory synapses, where it modulates glutamatergic neurotransmission, and elevated plasma or cerebrospinal fluid levels have been associated with early synaptic pathology, tau-related neurodegeneration, and cognitive decline in individuals progressing to Alzheimer's disease.[6,31] In contrast, neurodegenerative conditions are characterized by reduced cerebrospinal fluid and serum NPTX2 levels, which correlate with synaptic dysfunction, grey matter loss, and cognitive deterioration; mechanistically, NPTX2 regulates complement C1q activity and limits microglia-mediated synapse elimination, linking synaptic loss with neuroinflammatory processes.[34,35]

Beyond its role in neurodegeneration, NPTX1 has been implicated in post-stroke pathophysiology linking synaptic stress, inflammation, and vascular injury. Experimental ischemic stroke models show dynamic increases in serum and tissue NPTX1 after ischemia, with elevated levels exacerbating endothelial senescence, blood–brain barrier disruption, and brain injury processes central to post-stroke inflammation and long-term disability supporting its potential as a prognostic biomarker despite limited clinical data.[6,32,33] In parallel, emerging clinical evidence suggests that NPTX2 is relevant to post-stroke prognosis, particularly cognitive outcomes, as lower serum NPTX2 levels within 24 h of acute ischemic stroke are independently associated with post-stroke cognitive impairment at 3 months.[22] These findings indicate that while NPTX1 may primarily reflect inflammation-driven vascular pathology and neuronal stress, NPTX2 may index synaptic integrity and neuroinflammatory responses after stroke, together capturing complementary biological pathways that influence recovery and long-term prognosis.[22,35]

Shifting post-stroke prognostication from invasive and costly modalities such as MRI and cerebrospinal fluid analysis toward serum-based biomarkers offers substantial clinical and economic advantages. Blood sampling is minimally invasive, widely available, and can be performed rapidly and repeatedly, even in resource-limited settings, whereas MRI requires specialized infrastructure, trained personnel, and high operational costs, and CSF analysis involves invasive lumbar puncture with potential complications. Serum biomarkers can be measured early after stroke onset, allowing timely risk stratification, monitoring of disease progression, and individualized management without delaying care. Broad implementation of reliable blood-based prognostic markers would reduce dependence on high-cost imaging and invasive procedures, lower hospital expenditures, shorten diagnostic pathways, and decrease overall healthcare burden, particularly in high-volume stroke centers and low to middle-income countries where cost containment and accessibility are critical.

Future Vision on Post-Stroke Outcomes

Prognostic outcomes after stroke encompass mortality, functional disability, neurological recovery, and post-stroke complications, all of which reflect the complex biological cascade triggered by cerebral injury.[5,6,22] From a clinical perspective, incorporation of PTX3, NPTX1, and NPTX2 into prognostic assessment could enable earlier risk stratification in the acute stroke setting. Elevated PTX3 levels have been associated with worse functional outcomes and higher mortality, suggesting its utility in identifying patients at risk of severe disability or death.[4] Meanwhile, alterations in NPTX1 and NPTX2 may reflect synaptic damage and impaired neural network recovery, with potential relevance for predicting cognitive impairment and neurological recovery trajectories.[6,7,22,35]

Despite this promise, the existing evidence still has substantial limitations. Studies evaluating PTX3, NPTX1, and NPTX2 are characterized by marked heterogeneity in assay platforms and analytical methods, resulting in variability across reported concentrations. Cut-off values for defining high or low-risk patients are inconsistent, and sampling times range from hours to days after stroke onset, complicating comparisons and interpretation. These methodological inconsistencies limit the immediate clinical translation of these biomarkers into standardized prognostic tools. Moreover, human studies evaluating NPTX1 and NPTX2 in post-stroke patients remain limited, as most available evidence is derived from animal or proteomic studies. In contrast, there have been numerous studies on PTX-3 and acute post-stroke outcomes. Knowing that NPTX1 and NPTX2 come from the same protein family as PTX3, there is a knowledge gap we must fill in determining the complete biological profile of post-stroke patients to enhance post-stroke quality of life. Evidence for NPTX1 and NPTX2 remains preliminary and largely translational. While the scoping review utilized a comprehensive search across six databases, the sources indicate that potential language and publication bias persist due to the exclusion of grey literature and the inability to retrieve several relevant studies that lacked international publication

Looking ahead, future research directions should focus on harmonizing measurement protocols for PTX3, NPTX1, and NPTX2, including standardized timing of blood sampling and the use of validated, reproducible assay methods. The development of multimarker panels that integrate inflammatory markers (PTX3) with synaptic and neurodegenerative markers (NPTX1 and NPTX2) may better capture the multifactorial biology of stroke recovery than reliance on single biomarkers alone.

Conclusion

In conclusion, blood-based biomarkers demonstrate promising prognostic potential in post-stroke outcomes, with PTX3 showing the most consistent evidence to date. However, the current body of evidence remains heterogeneous, and data on other pentraxins such as NPTX1 and NPTX2 are still limited despite their shared biological lineage with PTX3. Large, well-designed prospective studies are therefore essential to validate these biomarkers and clarify their clinical utility in stroke prognosis.

Declaration of Interests

The authors declare no conflicts of interest.

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