



SYSTEMATIC REVIEW

Pre-Treatment Levels of Inflammatory Biomarkers as Predictors of Reperfusion Outcomes in Acute Ischemic Stroke: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Acute ischemic stroke (AIS) remains a major cause of disability and death despite effective reperfusion therapies, intravenous thrombolysis (IVT) and mechanical thrombectomy (MT). Systemic inflammation critically shapes ischemic injury and recovery, but the prognostic value of inflammatory biomarkers in reperfused patients is unclear, and previous reviews have not consistently addressed pre-treatment inflammatory markers in patients treated with IVT or MT.

István Szegedi and Zsolt Éles contributed equally to this work and share first authorship.

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Methods: We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Cochrane Library, Web of Science, and Scopus were searched through November 30, 2024, for studies assessing associations between circulating inflammatory biomarkers measured before IVT or MT and 3-month functional outcome (modified Rankin Scale, mRS). Data were pooled using random-effects models, with odds ratios (OR) and 95% confidence intervals (CI) calculated for poor outcome (mRS 3–6).

Results: Thirty-seven studies (8780 patients) met inclusion criteria; ten contributed to meta-analysis. Four biomarkers were evaluable in IVT-treated cohorts. Higher pre-treatment interleukin-6 (IL-6) predicted poor outcome (pooled OR 1.80, 95% CI 1.42–2.28), as did osteopontin (pooled OR 3.36, 95% CI 1.95–5.80). Tumor necrosis factor- α (TNF- α) showed a borderline association (pooled OR 1.05, 95% CI 1.00–1.10), whereas C-reactive protein (CRP) was not predictive (pooled OR 1.02, 95% CI 0.99–1.06).

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Evidence in MT cohorts was limited and heterogeneous.

Conclusion: Among patients with AIS treated with IVT, pre-treatment IL-6 showed the most consistent association with poor 3-month functional outcome, whereas CRP showed no reliable prognostic association. Osteopontin emerged as a promising but preliminary candidate biomarker based on limited evidence, and TNF- α showed only modest prognostic relevance. Evidence in patients undergoing MT remains insufficient for quantitative conclusions. Larger standardized prospective studies are needed to validate inflammatory biomarkers and determine their added prognostic value beyond established clinical and imaging predictors.

PLAIN LANGUAGE SUMMARY

Stroke is a major cause of death and long-term disability. Treatments such as intravenous thrombolysis and mechanical thrombectomy can restore blood flow in the brain, but even with timely treatment, many patients still experience poor recovery or die. This makes it important to identify early, simple markers that can help doctors estimate a patient's prognosis soon after hospital admission. Inflammation plays an important role in brain injury after stroke, especially when blood flow is restored. Substances in the blood, such as inflammatory proteins and signaling molecules, may reflect how strongly the body is reacting to the stroke. In this study, we reviewed and combined results from previously published research to examine whether these inflammatory markers, measured before treatment, are linked to patient outcomes after thrombolysis or thrombectomy. We found that higher levels of certain inflammatory markers—particularly interleukin-6 and osteopontin—were associated with a greater risk of poor recovery after thrombolysis. In contrast, other commonly used markers, such as C-reactive protein, did not show a clear relationship with outcomes. Evidence in patients treated with thrombectomy was limited and less consistent. These findings suggest that some inflammatory markers may help identify patients at higher risk

of poor outcomes early in their care. Because these markers can be measured from routine blood samples, they could potentially complement clinical assessment and brain imaging. However, larger and more standardized studies are needed before they can be routinely used in clinical practice.

Keywords: Acute ischemic stroke; Intravenous thrombolysis; Mechanical thrombectomy; Reperfusion therapy; Inflammatory biomarkers; Cytokines; Chemokines; Therapeutic outcome

Key Summary Points

Why carry out this study?

Acute ischemic stroke remains a leading cause of long-term disability and mortality, and outcome prediction before reperfusion therapy is still limited in clinical practice. Inflammatory processes critically influence ischemia–reperfusion injury, yet the prognostic value of baseline circulating inflammatory biomarkers in this setting remains uncertain.

We conducted a systematic review and meta-analysis to determine whether pre-treatment inflammatory biomarkers are associated with 3-month outcomes in patients treated with intravenous thrombolysis or mechanical thrombectomy.

What was learned from the study?

Higher baseline levels of interleukin-6 and osteopontin were strongly linked to unfavorable functional outcomes after thrombolysis, whereas tumor necrosis factor- α showed limited predictive value and C-reactive protein demonstrated no meaningful association.

These results suggest that selected inflammatory biomarkers may improve early prognostic assessment, but also highlight substantial gaps in evidence—particularly in thrombectomy populations—requiring well-designed prospective validation and multimodal model integration.

INTRODUCTION

Acute ischemic stroke (AIS) remains a leading cause of death and disability worldwide. Timely reperfusion strategies—intravenous thrombolysis (IVT) and mechanical thrombectomy (MT)—have revolutionized treatment, providing the best opportunity for functional recovery when initiated promptly [1]. However, despite successful recanalization, patient outcomes remain heterogeneous, with substantial variability in functional recovery, risk of mortality, and susceptibility to complications such as hemorrhagic transformation (HT) [2]. This highlights the urgent need for prognostic biomarkers that can refine patient selection, guide therapeutic decisions, and improve risk stratification in the acute setting.

Beyond vascular occlusion and reperfusion, systemic inflammation has emerged as a central determinant of stroke etiology, progression, and outcome [3, 4]. Cytokines, chemokines, adhesion molecules, and other inflammatory mediators are key modulators of ischemic brain injury, influencing endothelial integrity, blood–brain barrier disruption, and thromboinflammation [5, 6]. Their circulating levels can be measured with established laboratory techniques, and accumulating evidence suggests that several inflammatory biomarkers may hold prognostic relevance in AIS.

Observational studies have investigated associations between various cytokines and clinical outcomes following AIS, including functional independence, mortality, and HT. Among the most studied are C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor- α (TNF- α), while other mediators such as chemokines, adhesion molecules, and other acute-phase proteins have also been implicated. However, findings remain inconsistent, likely reflecting differences in study design, timing of biomarker assessment, definitions of outcomes, and adjustment for confounding variables.

Despite extensive research on inflammation in stroke, few reviews have concentrated on pre-treatment inflammatory markers in patients treated with reperfusion therapies (IVT and/or MT), where the dynamics

of ischemia–reperfusion injury may critically influence biomarker behavior and prognostic value [7, 8]. Given that reperfusion triggers both protective and injurious inflammatory responses, a focused evaluation of these processes in this context is especially important.

To address this gap, we performed a systematic review and meta-analysis of available evidence on the association between circulating inflammatory biomarkers and clinical outcomes in patients with AIS undergoing IVT or MT.

METHODS

The study methodology was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9]. The review protocol was registered on the Open Science Framework (OSF), providing a permanent, time-stamped public record of the methodology (<https://doi.org/10.17605/OSF.IO/B42CW>).

Search Strategy

We conducted a comprehensive search across several online databases, including PubMed (MEDLINE), the Cochrane Library, Web of Science, and Scopus. Our focus was on studies assessing cytokines, chemokines, and other circulating inflammatory biomarkers measured in peripheral blood prior to reperfusion therapy in patients with AIS, and their association with long-term functional outcomes. A detailed description of the applied search strategy and database-specific filters is provided in the Supplementary Material. No publication date restrictions were applied. The search was finalized on November 30, 2024.

Study Selection

The review question and eligibility criteria were structured according to the PICOTS framework for prognostic factor studies [10]. Briefly, the population comprised adult patients with acute

ischemic stroke treated with reperfusion therapy; the index prognostic factors were circulating inflammatory biomarkers measured before treatment; outcomes included poor functional outcome, mortality, hemorrhagic transformation, and symptomatic intracerebral hemorrhage; timing referred to pre-treatment biomarker assessment and primarily 3-month or 90-day clinical outcome assessment; and the setting was acute hospital-based reperfusion-treated stroke care.

Eligible studies were required to meet the following inclusion criteria: (1) enrollment of adult patients (age ≥ 18 years) with acute ischemic stroke who underwent recanalization therapy (IVT or MT); (2) imaging used to exclude intracranial hemorrhage and confirm ischemic stroke; (3) investigation of the relationship between venous blood inflammatory biomarkers and clinical outcomes; (4) blood samples collected prior to recanalization therapy; (5) clinical outcome reported using the modified Rankin Scale (mRS). To ensure comparability across studies, poor functional outcome for the quantitative synthesis was defined as an mRS score of 3–6, or equivalently $\text{mRS} > 2$, at 3 months or 90 days after stroke onset. Studies using substantially different dichotomizations of functional outcome, such as mRS 4–6, were recorded and presented descriptively in the tables but were not included in the meta-analysis [11]. The primary time point of interest was 3 months (or 90 days) after stroke onset, and only studies reporting outcomes at this time point were included in the quantitative synthesis. Studies assessing functional outcome at other follow-up durations were also recorded and are presented descriptively in the tables. Exclusion criteria were as follows: reviews, conference abstracts, case reports, editorials, and letters. Studies not published in English and animal studies were also excluded. Duplicates were removed using EndNote reference management software. During the initial screening, two independent reviewers (IS and ZBÉ) evaluated titles and abstracts. Full texts of potentially relevant papers were retrieved, and final eligibility was determined through full-text review. Any disagreements were resolved by discussion and consensus.

Ethical Approval

This article is based exclusively on previously published research and did not involve any new data collection from human participants or animals conducted by the authors.

Data Extraction

Two investigators (IS and ZBÉ) independently extracted the relevant information. The following data items were collected: type of recanalization therapy, inflammatory biomarkers investigated, first author and year of publication, sample size, time of outcome assessment, definition of clinical outcome and number of patients with assessed outcome, odds ratios (OR) with corresponding 95% confidence intervals (CI) for the association between biomarkers and outcomes, confounders adjusted for in the statistical models, and the number of patients receiving both thrombolytic and endovascular treatment. If studies included patients treated with and without recanalization, only data from the recanalization subgroup were considered. In studies assessing multiple biomarkers, each biomarker was analyzed separately. If outcomes were reported at multiple time points, all were extracted. In addition to functional outcome, we also recorded secondary endpoints such as mortality and intracerebral hemorrhage (ICH). The included studies and their data were categorized into two main groups and one smaller group based on whether patients received IVT, MT, or reperfusion treatment in general.

Quality Assessment

The quality of each study was appraised using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [12]. The checklist, provided in the Supplementary Material, consists of 15 items rated as yes (+), no (–), or unclear (?), with a maximum score of 15. For each study, the total quality score was calculated by summing the number of items rated as “yes.” All eligible studies were included in this review regardless of their quality rating.

Although QUADAS was originally developed for diagnostic accuracy studies, this modified tool was selected because the present review required structured assessment of several domains related to diagnostic confirmation, biomarker measurement, blinding, and clinical endpoint ascertainment. Items were adapted to the context of prognostic biomarker studies.

Statistical Analysis

For the quantitative synthesis, study-specific odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were extracted from individual studies for the association between pre-treatment inflammatory biomarkers and poor functional outcome. For the quantitative synthesis, poor functional outcome was defined as a modified Rankin Scale (mRS) score of 3–6, or equivalently mRS > 2, at 3 months or 90 days after stroke onset. Studies using substantially different dichotomizations of functional outcome, such as mRS 4–6, were recorded and summarized descriptively but were not included in the meta-analysis. No new effect size calculations were performed from raw data.

The quantitative synthesis was based on odds ratios reported in the original studies. These estimates were extracted as reported, and no additional adjustment or recalculation from raw data was performed. Information on covariate adjustment in the original studies was extracted descriptively where available and is presented in the study summary tables.

Effect estimates were extracted according to the scale reported in the original publications, including continuous, log-transformed, or categorical biomarker definitions. Because individual participant data were not available, biomarker effects could not be standardized to a common exposure scale across studies. Therefore, pooled ORs should be interpreted as summary estimates of association rather than directly interchangeable measures of prognostic effect.

For each biomarker, pooled estimates were calculated using a random-effects model with the DerSimonian–Laird method, given the expected clinical and methodological heterogeneity across studies. Between-study heterogeneity was

assessed using Cochran’s Q test and quantified with the I^2 statistic, with values > 50% considered to indicate substantial heterogeneity.

Potential publication bias was explored visually using funnel plots, in which the log OR was plotted against its standard error. No formal tests for funnel plot asymmetry, such as Egger’s regression, were performed, because the number of included studies per biomarker was below the recommended threshold for reliable testing.

Given the heterogeneity of the included studies, pooled estimates were interpreted cautiously. All analyses were performed with Stata 17 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study Selection

The database search initially retrieved 2434 records. After duplicate removal, 2154 articles were screened based on titles and abstracts (Fig. 1). Of these, 130 publications underwent full-text review, resulting in 37 studies that fulfilled the inclusion criteria for the systematic review: 26 focusing on IVT [13–38], 10 on MT [39–48], and one addressing reperfusion therapy in general [49]. Based on the quality assessment, only 10 of the 37 studies provided sufficiently comparable outcome definitions and effect estimates for inclusion in the meta-analysis, covering four biomarkers: CRP, IL-6, TNF- α , and osteopontin. All included studies were conducted in IVT-treated patients. Only studies reporting poor functional outcome as mRS 3–6 or mRS > 2 at 3 months or 90 days were included in the quantitative synthesis. Studies using different outcome thresholds, including mRS 4–6, were summarized descriptively but excluded from pooling. Outcome data regarding mortality and hemorrhagic transformation were insufficient to allow quantitative synthesis. None of the MT studies were suitable for meta-analysis due to heterogeneity in study design, biomarker assessment, and outcome reporting.

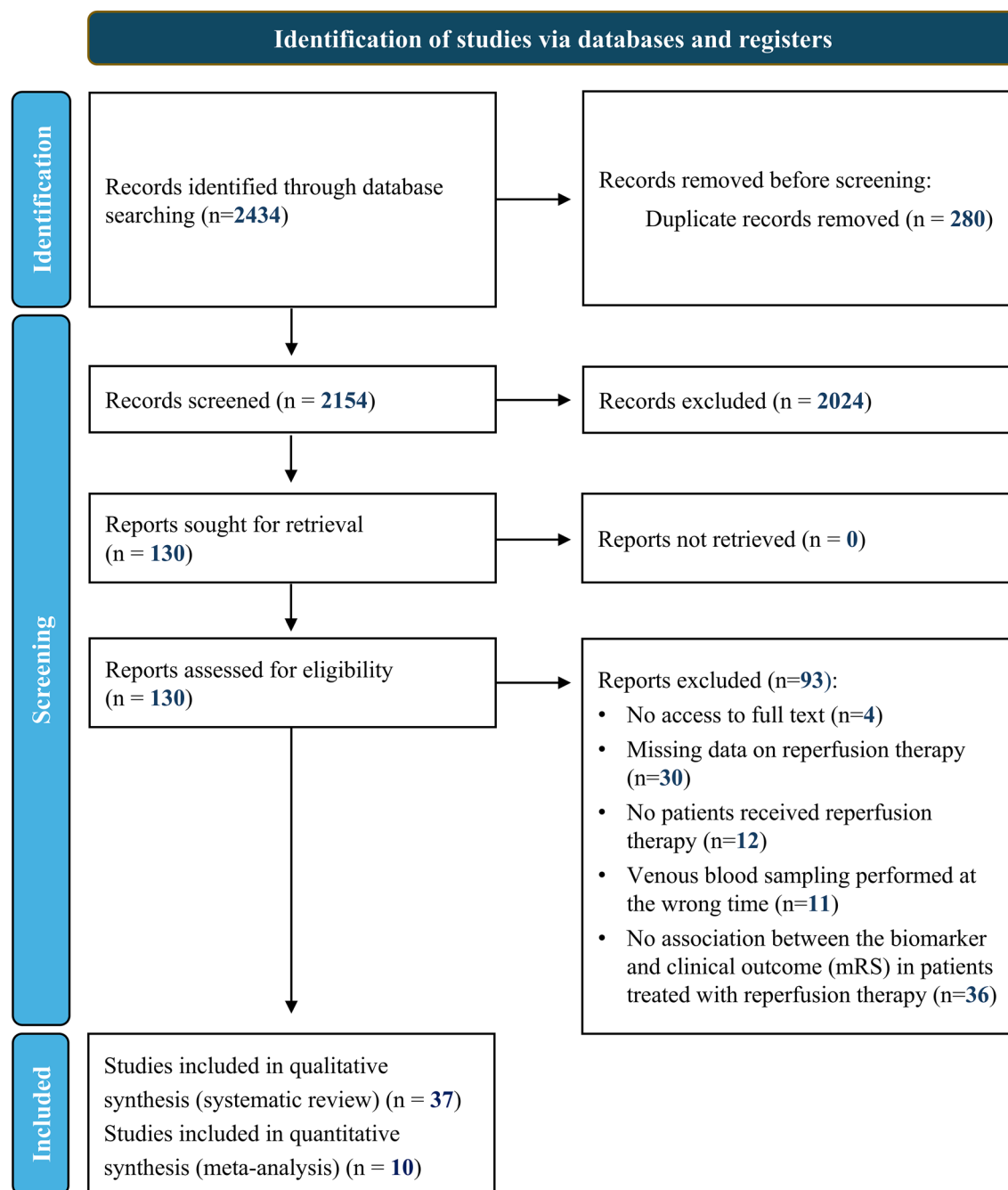


Fig. 1 PRISMA flowchart of literature search and study selection. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study Characteristics

Thirty-seven studies, including 8780 patients (6682 patients treated with IVT, 1886 patients

treated with MT, and 212 patients treated with general reperfusion therapy), reported a total of 26 different inflammatory biomarkers. Due to the large number of biomarkers, we divided

them into subgroups, such as acute-phase proteins, sepsis markers, cytokines, chemokines, neutrophil extracellular trap (NET)-related markers, cell surface activation and adhesion molecules, and vascular inflammation and tissue remodeling markers. In the context of IVT, the analyzed biomarkers included C-reactive protein (CRP) (16 studies), serum amyloid A (SAA) (1), IL-11 (1), IL-10 (1), IL-6 (6), tumor necrosis factor- α (TNF- α) (5), IL-38 (1), monocyte chemoattractant protein-1/C-C motif chemokine ligand 2 (MCP-1/CCL2) chemokine (1), regulated upon activation, normal T cell expressed and secreted/C-C motif chemokine ligand 5 (RANTES/CCL5) (1), neutrophil-elastase (NE) (1), myeloperoxidase (MPO) (1), cell-free DNA (1), vascular cell adhesion molecule 1 (VCAM-1) (1), intercellular adhesion molecule 1 (ICAM-1) (1), platelet endothelial cell adhesion molecule 1 (PECAM-1) (1), CD40 ligand (CD40L) (1), osteopontin (2), cystatin C (1), matrix metalloproteinase (MMP)-2 (1), MMP-3 (1), MMP-9 (3), pro-MMP-10 (1), MMP-13 (1), and endostatin (1), reported in a total of 26 publications (Table 1). The following 10 publications were analyzed in relation to endovascular therapy (thrombectomy): CRP (9), SAA (1), procalcitonin (1), IL-6 (2), MCP-1/CCL2 (1), MMP-9 (1), and vascular endothelial growth factor (VEGF) (1) (Table 2). One study did not specify which reperfusion therapy was used in patients, but two inflammatory biomarkers—IL-6 and TNF- α —were examined in relation to long-term outcome (Table S1). Detailed information on the measurement units and assay platforms used for inflammatory biomarker assessment across the included reperfusion therapy studies is provided in Table S2. The sample size of the included studies varied between 29 and 1242 participants. Thirteen studies provided data on more than one inflammatory biomarker. All studies assessed functional outcomes using the modified Rankin Scale (mRS), while some also reported additional outcomes, including hemorrhagic transformation (HT), symptomatic intracerebral hemorrhage (sICH), and mortality. In most cases, unfavorable outcome was defined as an mRS score >2 at 3 months or 90 days. In several studies, clinical outcomes were examined at multiple time points. Overall, four studies reported mRS

outcomes at discharge, 36 studies at 3 months or 90 days, two studies at 1 year, and one study assessed clinical outcomes at 3 years following stroke onset. Among the publications related to MT, all studies reported the proportion of patients who also received additional IVT. In contrast, 23 of the publications related to IVT did not report whether MT was performed or explicitly listed it as an exclusion criterion.

Quality Assessment

The quality of the included studies was generally moderate, with a median score of 8 out of a possible 15 points (range 5–11) (Supplementary Material). All 37 studies confirmed stroke diagnosis through expert evaluation and neuroimaging, applied the same diagnostic procedures to all participants, and did not use biomarkers to define clinical endpoints. Only seven studies documented blinding of biomarker measurements, and six reported blinding of clinical data collection. Eight studies did not specify whether all participants completed follow-up or did not provide reasons for withdrawal. Predefined biomarker cutoff values for outcome prediction were applied in just two studies. Conflict-of-interest statements were absent or declared as “none” in 33 reports. Nineteen studies were prospective, while five failed to provide at least two essential details, such as the study period, end of follow-up, or median follow-up time. All studies clearly prespecified clinical endpoints, and only two included a sample size calculation. Thirty studies reported a list of candidate variables with corresponding effect estimates (OR and 95% CI) for multivariate analyses; however, in nine of these, the inflammatory biomarker under investigation was not included in the model. Twenty-two studies specified the assay methodology.

Association Between IL-6 and 3-Month Poor Outcome After Intravenous Thrombolysis

Three studies comprising a total of 581 patients evaluated the prognostic significance of IL-6 (Fig. 2) [18, 24, 30]. The pooled OR was 1.80 (95% CI 1.42–2.28), showing a robust and statistically significant association between

Table 1 Summary of studies investigating inflammatory biomarkers and clinical outcomes following intravenous thrombolysis in acute ischemic stroke

Intravenous thrombolysis									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, n (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Acute-phase proteins	Chang et al. (2023)	405	Only IVT (EVT excluded)	3 months	mRS 3–6	121 (29.8)	Adjusted	1.025 (0.839–1.364)	SVO, cardioembolism, basal ganglia, 3-month BI score, NIHSS score during hospitalization, 3-month NIHSS score, ASPECT score, infarct volume, EMR, NLR, WBC, and SAA
	Gensicke et al. (2013)	257	IVT (EVT status N/A)	3 months	mRS 2–6	163 (63.4)	–	–	–
				3 years	mRS 2–6	162 (63.0)	Adjusted	1.006 (0.984–1.030)	Age, NIHSS score, SBP, Charlson Comorbidity Index, CAD, AF, clinical stroke syndrome, 3-month outcome, epileptic seizures, and sICH (NINDS)
				3 years	Mortality (mRS 6)	75 (29.2)	–	–	–
				1.5–7 days	sICH	10 (3.9)	–	–	–
	İnanç et al. (2018)	129	IVT (EVT status N/A)	3 months	mRS 0–2	Not indicated	–	–	–
	Li et al. (2023)	404	IVT (EVT status N/A)	3 months	mRS 3–6	148 (36.6)	Adjusted	1.001 (0.999–1.003)	Age, BMI, FBG, NIHSS, infarct volume, TC, TG, HDLC, LDL-C, IL-6, IL-11, and TNF-α
	Montaner et al. (2006)	143	IVT (EVT status N/A)	3 months	Mortality (mRS 6)	19 (13.2)	Adjusted	5.04 (1.51–16.83), CRP > 7.7 mg/L	Stroke severity
	Pawluk et al. (2020)	83	Only IVT (EVT excluded)	3 months	mRS 3–6	62 (74.7)	Adjusted	0.66 (0.30–1.43)	LCI, T2D, age, years, HT, PSI, NIHSS on admission
				Discharge	mRS 3–6	60 (72.3)	Adjusted	1.13 (0.71–1.80)	
	Rocco et al. (2015)	1242	IVT (EVT status N/A)	7 days	sICH	84 (6.8)	–	–	Model includes only the follow-up CRP
				3 months	mRS 3–5	404/1067 (37.9)	–	–	
				3 months	Mortality (mRS 6)	133/1067 (12.5)	–	–	
	Tiainen et al. (2013)	985	IVT (EVT status N/A)	3 months	mRS 3–6	403/959 (42.0)	Adjusted	1.07 (1.01–1.14) per 5 mg/L	Not indicated
				7 days	sICH	69 (7.0)	Adjusted	1.00 (0.92–1.09)	Age, NIHSS, glucose, dense artery sign, and early infarct sign

Intravenous thrombolysis

[illegible]

Table 1 continued

Intravenous thrombolysis									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, n (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Cytokines									
IL-11	Li et al. (2023)	404	IVT (EVT status N/A)	3 months	mRS 3–6	148 (36.6)	Adjusted	0.526 (0.346–0.799)	Age, BMI, FBG, NIHSS, infarct volume, TC, TG, HDLC, LDLC, IL-6, CRP, and TNF- α
IL-10	Rodríguez-Yanes et al. (2013)	184	Only IVT (EVT excluded)	3 months	mRS 0–2	103 (56.0)	Adjusted	1.07 (1.03–1.11)	Age, NIHSS, and DWI volume at admission
							Adjusted	3.14 (1.04–9.51), IL-10 $\geq$ 30 pg/mL	Age, NIHSS, and DWI volume at admission
IL-6	Li et al. (2023)	404	IVT (EVT status N/A)	3 months	mRS 3–6	148 (36.6)	Adjusted	1.891 (1.657–2.159)	Age, BMI, FBG, NIHSS, infarct volume, TC, TG, HDLC, LDLC, CRP, IL-11, and TNF- α
	Pawluk et al. (2022)	125	IVT (EVT status N/A)	Discharge	mRS 0–2	91/121 (75.2)	–	–	–
				3 months	mRS 0–2	85/113 (75.2)	–	–	–
				1 year	mRS 0–2	79/91 (86.8)	–	–	–
	Pawluk et al. (2020)	83	Only IVT (EVT excluded)	3 months	mRS 3–6	62 (74.4)	Adjusted	5.85 (1.46–23.48)	LCI, T2D, age, HT, PSI, NIHSS on admission
				Discharge	mRS 3–6	60 (72.3)	Adjusted	2.14 (1.19–3.84)	LCI, T2D, age, HT, PSI, NIHSS on admission
	Rodríguez-Yanes et al. (2013)	184	Only IVT (EVT excluded)	3 months	mRS 0–2	103 (56.0)	–	–	–
	Rodríguez et al. (2013)	76	IVT (EVT status N/A)	24–36 h	sICH	8 (10.5)	–	–	–
	Tang et al. (2024)	94	IVT (EVT status N/A)	3 months	mRS 3–6	35 (37.2)	Adjusted	1.623 (1.282–1.933)	Pre-treatment NIHSS scores, serum LDL levels, and serum TNF- α
Tumor necrosis factor- α (TNF- α)	Li et al. (2023)	404	IVT (EVT status N/A)	3 months	mRS 3–6	148 (36.6)	Adjusted	1.017 (0.982–1.054)	Age, BMI, FBG, NIHSS, infarct volume, TC, TG, HDLC, LDLC, IL-6, IL-11, and CRP

Table 1 continued

Intravenous thrombolysis									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with outcome, n (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Chemokines	Pawluk et al. (2022)	125	IVT (EVT status N/A)	Discharge	mRS 0–2	91/121 (75.2)	–	–	–
				3 months	mRS 0–2	85/113 (75.2)	–	–	–
				1 year	mRS 0–2	79/91 (86.8)	–	–	–
	Rodríguez-Yanes et al. (2013)	184	Only IVT (EVT excluded)	3 months	mRS 0–2	103 (56.0)	–	–	–
	Rodríguez et al. (2013)	76	IVT (EVT status N/A)	3 months	mRS 3–6	Not indicated	Adjusted	1.21 (1.02–1.53)	Age, history of AF, glucose levels, basal NIHSS, END, hypodensity volume, and early CT signs of infarction
	Tang et al. (2024)	94	IVT (EVT status N/A)	3 months	mRS 3–6	35 (37.2)	Adjusted	1.055 (1.024–1.088)	Pre-treatment NIHSS scores, serum LDL levels, and serum IL-6
	Zara Rafe et al. (2021)	29	IVT (EVT status N/A)	3 months	mRS 3–6	17 (58.6)	–	–	–
	Mesquer et al. (2020)	151	Mixed (EVT $n = 55$), only EVT $n = 28$, mechanical EVT $n = 54$	3 months	mRS 0–1	64 (42.4)	Adjusted	0.92 (0.62–1.37)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.96 (0.63–1.44)	
	Pawluk et al. (2023)	125	IVT (EVT status N/A)	Discharge	mRS 0–2	91/121 (75.2)	–	–	–
RANTES (CCL5)				3 months	mRS 0–2	85/113 (75.2)	–	–	–
				1 year	mRS 0–2	79/91 (86.8)	–	–	–

Table 1 continued

Intravenous thrombolysis									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, n (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
NET markers	Li et al. (2023)	146	Mixed (EVT <i>n</i> = 27), only EVT <i>n</i> = 30	3 months	mRS 3–6	25/119 (21.0)	Adjusted	8.931 (2.330–34.238), NE > 177.22 ng/mL	Sex, age, OTT, stroke severity, AF, serum glucose, NLR, and PR3
Myeloperoxidase	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1	64 (42.4)	Adjusted	0.60 (0.37–0.97)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.53 (0.31–0.89)	
Cell-free DNA	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1	64 (42.4)	Adjusted	0.76 (0.49–1.17)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.23 (0.08–0.66)	
Cell surface activation and adhesion molecules	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1	64 (42.4)	Adjusted	0.54 (0.33–0.89)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.53 (0.31–0.90)	
ICAM-1	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1	64 (42.4)	Adjusted	0.59 (0.37–0.92)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.67 (0.40–1.10)	
PECAM-1	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1	64 (42.4)	Adjusted	0.74 (0.47–1.15)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	1.01 (0.63–1.62)	
CD40L	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1	64 (42.4)	Adjusted	0.65 (0.41–1.02)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.80 (0.50–1.28)	

Table 1 continued

Intravenous thrombolysis									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, n (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Vascular inflammation and tissue remodeling markers	Ortoe-pontin (OPN)	Meseguer et al. (2020)	151	3 months	mRS 0–1	64 (42.4)	Adjusted	0.49 (0.29–0.81)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.34 (0.18–0.62)	
	Mendiroz et al. (2011)	178	IVT (EVT status N/A)	3 months	mRS 3–6	72/130 (55.4)	Adjusted	5.01 (1.6–15.72), OPN > 27.22 ng/mL	Gender, age, hypertension, dyslipidemia, DM, tobacco use, AF, CHD, previous stroke, pre-treatment NIHSS, atherothrombotic disease, and occlusion location
					mRS 0–1	64 (42.4)	Adjusted	0.89 (0.55–1.44)	
	Cystatin C	Meseguer et al. (2020)	151	3 months	mRS 0–2	80 (53.0)	Adjusted	0.61 (0.36–1.05)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–1	64 (42.4)	Adjusted	1.19 (0.74–1.89)	
Matrix metalloproteinase-2 (MMP-2)	Meseguer et al. (2020)	151	Mixed (EVT $n=55$), only EVT $n=28$, mechanical EVT $n=54$	3 months	mRS 0–1	64 (42.4)	Adjusted	1.19 (0.74–1.89)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	1.34 (0.82–2.19)	
	Matrix metalloproteinase-3 (MMP-3)	Meseguer et al. (2020)	151	3 months	mRS 0–1	64 (42.4)	Adjusted	1.03 (0.67–1.56)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
					mRS 0–2	80 (53.0)	Adjusted	0.95 (0.60–1.51)	

Table 1 continued

Intravenous thrombolysis									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with outcome, n (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Matrix metalloproteinase-9 (MMP-9)	Rodríguez et al. (2013)	76	IVT (EVT status N/A)	24–36 h	sICH	8 (10.5)	–	–	–
	Rodríguez-Yanes et al. (2013)	184	Only IVT (EVT excluded)	3 months	mRS 0–2	103 (56.0)	–	–	–
	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1 mRS 0–2	64 (42.4) 80 (53.0)	Adjusted Adjusted	0.90 (0.60–1.34) 0.67 (0.42–1.05)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
Pro-matrix metalloproteinase-10 (pro-MMP10)	Rodríguez et al. (2013)	76	IVT (EVT status N/A)	3 months	mRS 3–6	Not indicated	Adjusted	1.61 (1.09–2.17)	Age, history of AF, glucose levels, basal NIHSS, END, hypodensity volume, and early CT signs of infarction
				24–36 h	sICH	8 (10.5)	–	–	–
Matrix metalloproteinase-13 (MMP-13)	Meseguer et al. (2020)	151	Mixed (EVT <i>n</i> = 55), only EVT <i>n</i> = 28, mechanical EVT <i>n</i> = 54	3 months	mRS 0–1 mRS 0–2	64 (42.4) 80 (53.0)	Adjusted Adjusted	0.83 (0.52–1.32) 0.86 (0.54–1.37)	Age, admission NIHSS, documented occlusion (none vs. ICA occlusion vs. other arterial occlusion), and AIS treatments (including IVT ± EVT approach)
	Navarro-Sobrinho et al. (2011)	109	IVT (EVT status N/A)	3 months	mRS 3–6	50 (45.9)		8.9 (2.7–28.8) ≥ 184 ng/mL	Age, previous stroke, DBP, atherothrombotic etiology and stroke severity

Table 1 continued

<i>AF</i> atrial fibrillation, <i>AIS</i> acute ischemic stroke, <i>ASPECT</i> Alberta Stroke Program Early CT Score, <i>BI score</i> Barthel Index score, <i>BMI</i> body mass index, <i>CAD</i> coronary artery disease, <i>Cav-1</i> caveolin-1, <i>CCL2</i> (MCP-1) C–C motif chemokine ligand 2 (monocyte chemoattractant protein-1), <i>CCL5</i> (RANTES) C–C motif chemokine ligand 5 (regulated on activation normal T cell expressed and secreted), <i>CD40L</i> CD40 ligand, <i>CHD</i> coronary heart disease, <i>CI</i> confidence interval, <i>CRP</i> /hs-CRP C-reactive protein/high-sensitivity C-reactive protein, <i>CT</i> computed tomography, <i>DBP</i> diastolic blood pressure, <i>DM</i> diabetes mellitus, <i>DNT</i> door-to-needle time, <i>DWT</i> volume diffusion-weighted imaging lesion volume, <i>EMR</i> emergency medical response, <i>END</i> early neurological deterioration, <i>EVT</i> endovascular treatment, <i>FBG</i> fasting blood glucose, <i>HDL</i> C high-density lipoprotein cholesterol, <i>HT</i> hemorrhagic transformation, <i>ICA</i> internal carotid artery, <i>ICAM-1</i> intercellular adhesion molecule 1, <i>IL</i> interleukin, <i>INR</i> international normalized ratio, <i>IPI</i> inflammation prognostic index, <i>IVT</i> intravenous thrombolysis, <i>LCI</i> lacunar cerebral infarct, <i>LDL</i> low-density lipoprotein, <i>LDLC</i> low-density lipoprotein cholesterol, <i>MMP</i> matrix metalloproteinase, <i>mRS</i> Modified Rankin Scale, <i>MT</i> mechanical thrombectomy, <i>N/A</i> not available, <i>NE</i> neutrophil elastase, <i>NET</i> neutrophil extracellular trap, <i>NGB</i> neuroglobin, <i>NIHSS</i> National Institutes of Health Stroke Scale, <i>NLR</i> neutrophil-to-lymphocyte ratio, <i>ONT</i> onset-to-needle time, <i>OPN</i> osteopontin, <i>OTT</i> onset-to-treatment time, <i>PECAM-1</i> platelet endothelial cell adhesion molecule 1, <i>PR3</i> proteinase 3, <i>PSI</i> post-stroke infection, <i>PT</i> prothrombin time, <i>RBC</i> red blood cell, <i>SAA</i> serum amyloid A, <i>SBP</i> systolic blood pressure, <i>SIRI</i> systemic inflammation response index, <i>SVO</i> small vessel occlusion, <i>T2D</i> type 2 diabetes, <i>TC</i> total cholesterol, <i>TG</i> triglyceride, <i>TNF-α</i> tumor necrosis factor alpha, <i>UA</i> uric acid, <i>VCAM-1</i> vascular cell adhesion molecule 1, <i>WBC</i> white blood cell, <i>sICH</i> (NINDS) symptomatic intracerebral hemorrhage (National Institute of Neurological Disorders and Stroke criteria)

elevated IL-6 and worse outcomes. Substantial heterogeneity was observed ($I^2=59.5\%$, $p=0.084$), largely driven by one study with an imprecisely estimated strong effect. Nonetheless, the direction of association was consistently positive across all included studies. The findings highlight IL-6 as a promising inflammatory biomarker associated with poor clinical prognosis.

Association Between Osteopontin and 3-Month Poor Outcome After Intravenous Thrombolysis

Two studies, including 329 patients, examined the association between osteopontin levels and clinical outcome (Fig. 3) [20, 21]. The pooled OR was 3.36 (95% CI 1.95–5.80), indicating a strong and significant association between elevated osteopontin and unfavorable prognosis. No heterogeneity was detected ($I^2=0.0\%$, $p=0.436$), with both studies demonstrating consistent results in the same direction. Although the evidence is limited to two reports, the magnitude of effect suggests that osteopontin may serve as a promising biomarker of adverse outcome.

Association Between TNF-α and 3-Month Poor Outcome After Intravenous Thrombolysis

The prognostic role of TNF-α was investigated in three studies (Fig. 4), encompassing 574 patients [18, 28, 30]. The pooled OR was 1.05 (95% CI 1.00–1.10), representing a borderline significant association. Substantial heterogeneity was observed ($I^2=63.8\%$, $p=0.063$). Two studies demonstrated significant positive associations (OR=1.21, 95% CI 1.02–1.53; OR=1.06, 95% CI 1.02–1.09), while one reported no significant relationship (OR=1.02, 95% CI 0.98–1.05). Taken together, these findings suggest that TNF-α may contribute to poor functional outcome, although the overall effect remains modest and heavily influenced by the large neutral study.

Table 2 Summary of studies investigating inflammatory biomarkers and clinical outcomes following mechanical thrombectomy in acute ischemic stroke

Mechanical thrombectomy/endovascular therapy									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, <i>n</i> (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Acute-phase proteins	Huber et al. (2016)	56	Mixed (IVT <i>n</i> = 73 from 115 patients)	90 days	mRS 3–6	33 (58.9)	–	–	–
				90 days	Mortality (mRS 6)	13 (23.2)	–	–	–
	Mechtrouff et al. (2021)	164	Mixed (IVT <i>n</i> = 88)	3 months	mRS 3–6	46 (28.0)	Adjusted	1.03 (0.48–2.19)	Age, baseline NIHSS score, hypertension, IVT, intracranial ICA occlusion, and infarct growth
	Schuppner et al. (2018)	41	Mixed (IVT <i>n</i> = 39)	3 months	mRS 5–6	18 (43.9)	–	–	–
	Xiao et al. (2024)	238	Mixed (IVT <i>n</i> = 50)	3 months	mRS 3–6	93 (39.0)	–	–	–

Table 2 continued

Mechanical thrombectomy/endovascular therapy									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, <i>n</i> (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
	Yeh et al. (2023)	92	Mixed (IVT <i>n</i> = 28)	3 months	mRS 4–6	25 (27.2)	Adjusted	1.79 (1.09–2.93)	Sex, initial NIHSS score, infection at 24 h, and HT
					Mortality (mRS 6)	8 (8.7)	Adjusted	3.07 (1.23–7.66)	Initial NIHSS score, WBC, infection at 24 h, and malignant cerebral edema
	Du et al. (2023)	295	Mixed (IVT <i>n</i> = 101)	3 months	mRS 3–6	131 (44.4)	–	–	–
	Ozdogru et al. (2024)	103	Only EVT (IVT excluded)	3 months	mRS 3–6	55 (53.4)	–	–	–
	Oh et al. (2020)	411	Mixed (IVT <i>n</i> = 152)	3 month	mRS 3–6	199 (48.4)	–	–	–
				3 month	Mortality (mRS 6)	37 (9.0)	–	–	–
				7 days	HT	103 (25.0)	–	–	–
				Post-procedural	sICH	28 (6.8)	–	–	–

Table 2 continued

Mechanical thrombectomy/endovascular therapy									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, <i>n</i> (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Serum amyloid A (SAA)	Yi et al. (2021)	440	Mixed (IVT <i>n</i> = 159) Post-procedural	3 months	mRS 0–2	245 (55.7)	–	–	–
				14 days	sICH	32 (72.7)	–	–	–
				3 months	HT	103 (23.4)	–	–	–
	Yeh et al. (2023)	92	Mixed (IVT <i>n</i> = 28)	3 months	mRS 4–6	25 (27.2)	Adjusted	1.09 (1.02–1.17)	Sex, initial NIHSS score, infection at 24 h, and HT
				3 months	Mortality (mRS 6)	8 (8.7)	Adjusted	1.07 (0.96–1.18)	Initial NIHSS score, WBC, infection at 24 h, and malignant cerebral edema

Table 2 continued

Mechanical thrombectomy/endovascular therapy									
Biomarker	Author (year)	Sample size	Reperfusion therapy	Time of outcome assessment	Definition of clinical outcome	Patients with assessed outcome, <i>n</i> (%)	Model type	Odds ratio (95% CI)	Confounders included in the model
Sepsis markers	Procalcitonin (PCT)	Xiao et al. (2024)	238	Mixed (IVT <i>n</i> = 50)	3 months	mRS 3–6	93 (39.1)	–	–
	IL-6	Mechtrouff et al. (2021)	164	Mixed (IVT <i>n</i> = 88)	3 months	mRS 3–6	46 (28.0)	–	–
Cytokines and chemokines		Schuppner et al. (2018)	41	Mixed (IVT <i>n</i> = 39)	3 months	mRS 5–6	18 (43.9)	–	–
	CCL2 (MCP1)	Schuppner et al. (2018)	41	Mixed (IVT <i>n</i> = 39)	3 months	mRS 5–6	18 (43.9)	–	–
Vascular inflammation markers	Matrix metalloproteinase-9 (MMP-9)	Schuppner et al. (2018)	41	Mixed (IVT <i>n</i> = 39)	3 months	mRS 5–6	18 (43.9)	–	–
	VEGF	Xu et al. (2024)	46	Mixed (IVT <i>n</i> = 12)	3 months	mRS 3–6	24 (52.2)	Adjusted	1.037 (0.994–1.083)

CCL2 (MCP-1) C–C motif chemokine ligand 2 (monocyte chemoattractant protein-1), *CI* confidence interval, *CRP* C-reactive protein, *ELVT* endovascular treatment, *HT* hemorrhagic transformation, *ICA* internal carotid artery, *IL* interleukin, *IVT* intravenous thrombolysis, *MMP-9* matrix metalloproteinase 9, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *PCT* procalcitonin, *SAA* serum amyloid A, *sICH* symptomatic intracerebral hemorrhage, *VEGF* vascular endothelial growth factor, *WBC* white blood cell

Association Between CRP and 3-Month Poor Outcome After Intravenous Thrombolysis

Six studies with a combined sample size of 2119 patients assessed the relationship between C-reactive protein (CRP) levels and outcome (Fig. 5) [13, 18, 19, 24, 31, 37]. The pooled OR was 1.02 (95% CI 0.99–1.06), suggesting no significant relationship between elevated CRP and adverse prognosis. Heterogeneity was moderate ($I^2 = 48.2\%$, $p = 0.085$), reflecting some variability across studies. While

one study showed a clear positive association (OR=1.07, 95% CI 1.01–1.14), another demonstrated only a borderline effect (OR=1.05, 95% CI 1.00–1.10), whereas most studies reported null or inconsistent results. The overall direction of effect was weak and largely influenced by a high-weight study with no association, indicating that CRP may be a less reliable predictor in this setting.

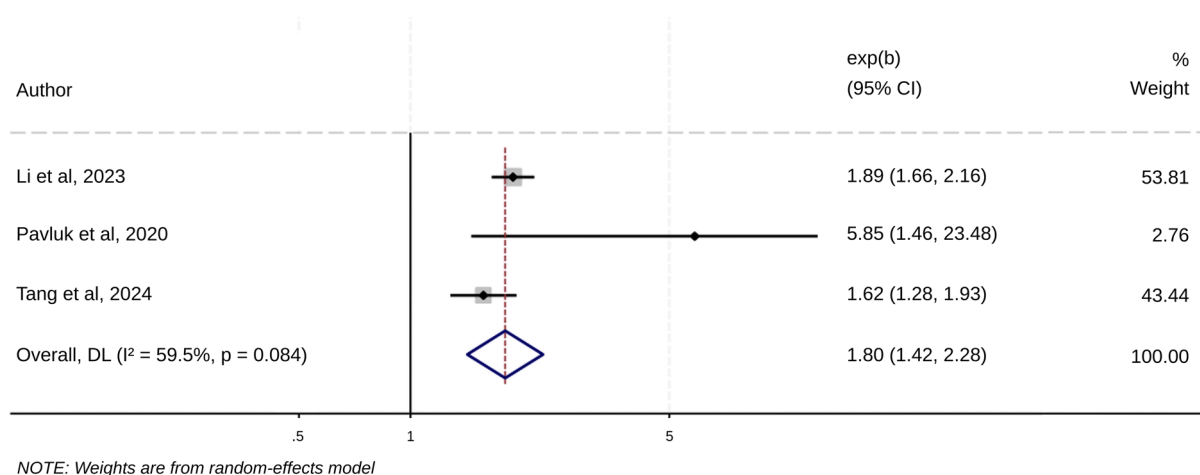


Fig. 2 Baseline IL-6 and poor functional outcome (mRS 3–6) 3 months after intravenous thrombolysis. *IL-6* interleukin-6, *mRS* modified Rankin Scale

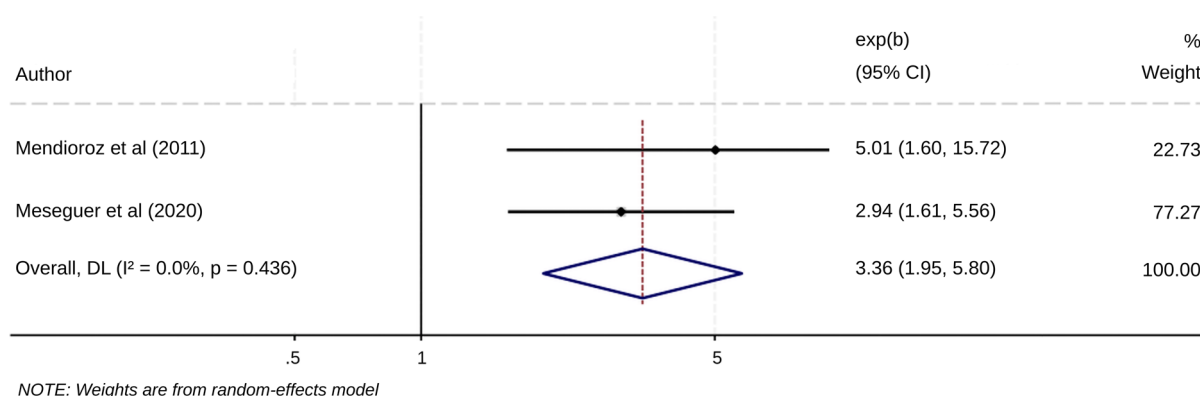


Fig. 3 Baseline osteopontin and poor functional outcome (mRS 3–6) 3 months after intravenous thrombolysis. *mRS* modified Rankin Scale

Publication Bias

Assessment of publication bias was only feasible for CRP, as this was the only biomarker with a sufficient number of studies. Given the limited dataset, no formal statistical tests were performed. Instead, visual inspection of the funnel plot (Fig. 6) was carried out. The plot appeared reasonably symmetric, suggesting no clear evidence of publication bias; however, interpretation remains restricted by the small number of studies included.

DISCUSSION

In this systematic review and meta-analysis, IL-6 showed the most consistent association with poor 3-month functional outcome after IVT among the biomarkers suitable for quantitative synthesis. Osteopontin also showed a strong association in the limited number of available studies, whereas TNF- α showed only a modest and borderline effect, and CRP did not demonstrate a reliable prognostic association. These findings should be interpreted cautiously given the predominantly observational evidence base and substantial heterogeneity in patient

populations, biomarker measurement, covariate adjustment, and outcome definitions.

IL-6 emerged as the most promising and reproducible prognostic biomarker in our analysis. Across all included studies, elevated baseline IL-6 levels were consistently associated with poor functional outcome, and the pooled effect estimate confirmed a strong and statistically significant relationship. IL-6 is a pleiotropic cytokine rapidly released after cerebral ischemia by neurons, glial cells, and endothelial cells. It activates JAK/STAT signaling, induces hepatic production of acute-phase proteins such as CRP, and promotes leukocyte recruitment, blood–brain barrier disruption, and infarct expansion [50, 51]. In the setting of reperfusion, elevated IL-6 levels likely reflect an exaggerated inflammatory response that amplifies ischemia–reperfusion injury, thereby limiting neurological recovery and functional outcome.

Osteopontin, an extracellular matrix glycoprotein with cytokine-like properties, emerged as a potentially valuable biomarker. It is expressed by neurons, glial cells, and endothelial cells after cerebral ischemia. It binds to integrins and CD44 receptors, mediating leukocyte recruitment, matrix remodeling, and blood–brain barrier disruption in the acute phase, while also participating in repair processes during recovery [52, 53]. Although evidence is currently limited to two studies, both demonstrated a strong and

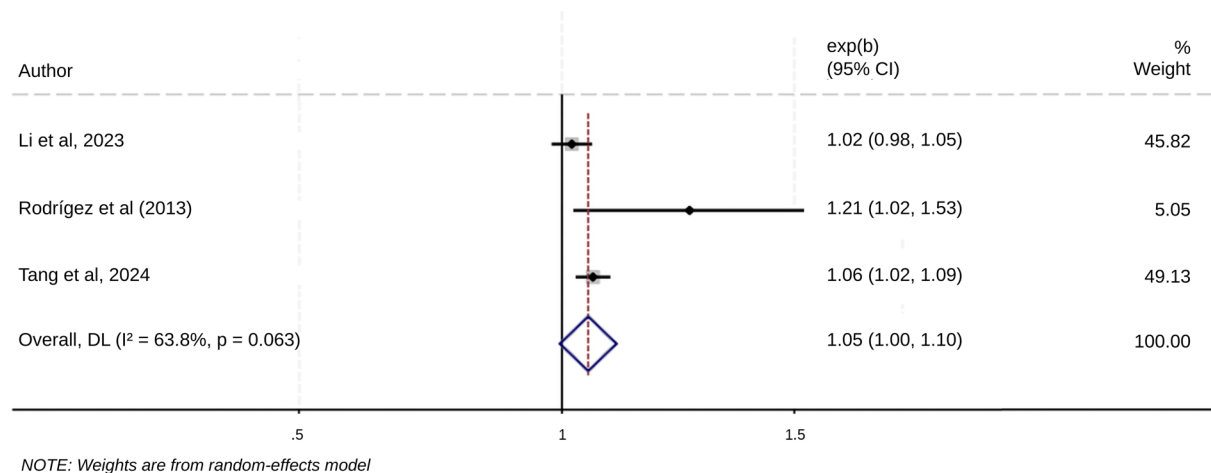


Fig. 4 Baseline TNF- α and poor functional outcome (mRS 3–6) 3 months after intravenous thrombolysis. TNF- α tumor necrosis factor- α , mRS modified Rankin Scale

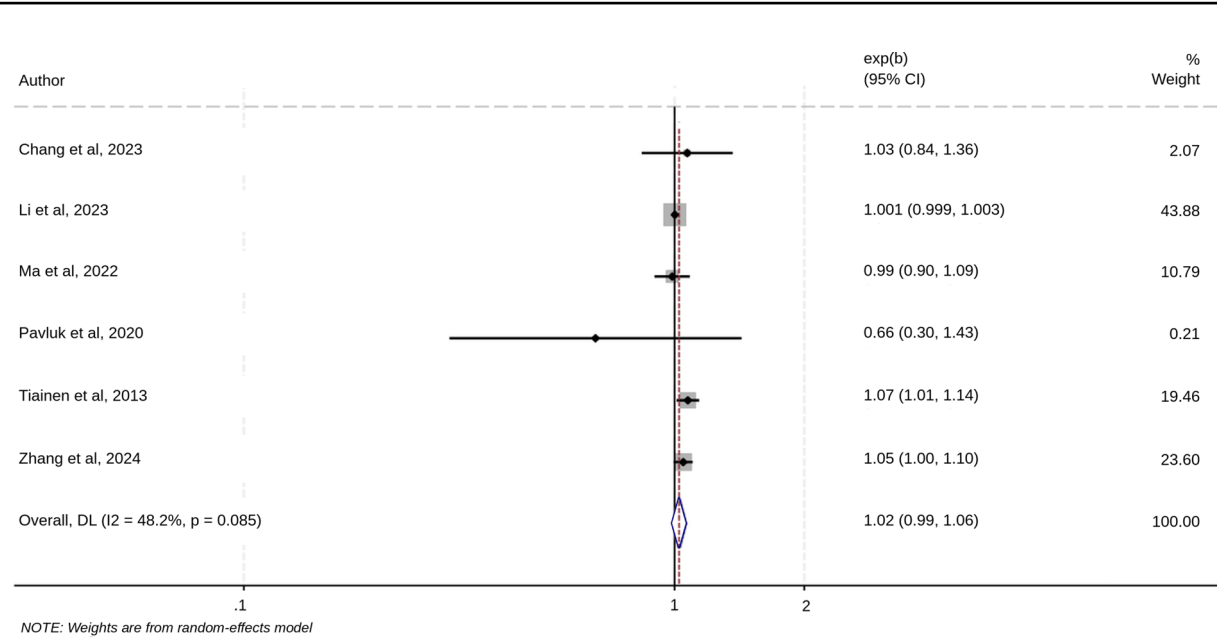


Fig. 5 Baseline CRP and poor functional outcome (mRS 3–6) 3 months after intravenous thrombolysis. *CRP* C-reactive protein, *mRS* modified Rankin Scale

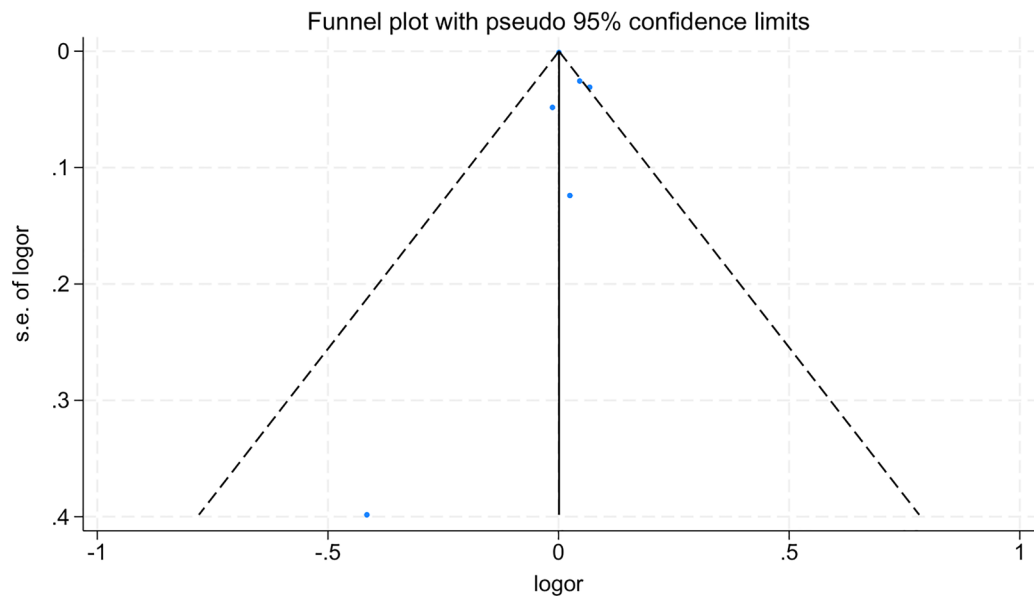


Fig. 6 Funnel plot of meta-analysis: baseline CRP and 3-month poor outcome (mRS 3–6) after intravenous thrombolysis. *CRP* C-reactive protein, *mRS* modified Rankin Scale

consistent association with poor 3-month functional outcome, and the absence of heterogeneity supports the importance of this finding. These results suggest that osteopontin may represent a powerful prognostic marker once validated in larger, prospective cohorts.

TNF- α is a proinflammatory cytokine produced by activated microglia, astrocytes, and infiltrating leukocytes in the ischemic brain. It promotes neuronal apoptosis, oxidative stress, and blood–brain barrier disruption through upregulation of adhesion molecules and matrix metalloproteinases, thereby amplifying ischemic and reperfusion injury [54, 55]. While two studies demonstrated significant associations with poor functional outcome, one large study reported neutral results, resulting in only a borderline pooled effect with substantial heterogeneity. These findings suggest that although TNF- α contributes to ischemic and reperfusion injury, its utility as a circulating prognostic biomarker is weaker and more context-dependent than that of IL-6.

CRP, as an acute-phase protein, is produced in the liver under the regulation of interleukin-6, and it plays a central role in systemic inflammation. Beyond serving as a biomarker, experimental studies suggest that CRP may contribute to ischemic injury by activating the complement cascade, enhancing leukocyte-endothelial interactions, and promoting endothelial dysfunction, thereby facilitating blood–brain barrier breakdown and secondary tissue damage [56, 57]. Despite these plausible mechanisms, our pooled analysis showed no significant association between CRP levels and 3-month outcomes after IVT and although a few studies suggested worse prognosis with higher CRP, these were outweighed by larger neutral studies. This indicates that CRP may reflect systemic inflammation without offering independent predictive information in the IVT setting.

Mechanistically, both IL-6 and osteopontin are closely involved in the neuroinflammatory response after ischemic stroke, although they may reflect partly different phases of injury. Following cerebral ischemia, damage-associated molecular pattern (DAMP)-mediated activation of resident glial cells, endothelial cells, and infiltrating leukocytes induces pro-inflammatory

cytokine release [58, 59]. IL-6 amplifies this response through NF- κ B- and JAK/STAT-related signaling, promoting leukocyte recruitment, blood–brain barrier disruption, oxidative stress, and secondary tissue injury [60]. On the other hand, osteopontin is upregulated in the peri-infarct and infarct core regions and participates in leukocyte adhesion, matrix remodeling, glial activation, and blood–brain barrier dysfunction, while also contributing to later repair mechanisms such as angiogenesis and neural progenitor cell migration [61, 62]. Thus, elevated circulating IL-6 and osteopontin may capture complementary aspects of post-ischemic neuroinflammation: IL-6 as a marker of acute inflammatory amplification, and osteopontin as a marker of inflammation-associated tissue remodeling and repair response.

Beyond the previously discussed biomarkers, several additional inflammatory and vascular markers have been investigated in IVT-treated patients, although most evidence derives from single studies with limited sample sizes. SAA showed the most consistent association with poor prognosis in a dose-dependent manner [13], while higher IL-10 and IL-11 levels were associated with more favorable outcomes [18, 29]. In contrast, findings for other cytokines and chemokines, including IL-38, MCP-1, and RANTES, were inconclusive or neutral [21, 26, 35].

Among NET-related markers, neutrophil elastase showed the clearest association with poor outcome [17], whereas myeloperoxidase and cell-free DNA yielded inconsistent findings, suggesting a possible adverse effect at some thresholds but null findings at others [21]. Adhesion and vascular remodeling markers also showed heterogeneous results: VCAM-1, ICAM-1, pro-MMP-10, and endostatin were linked to worse outcomes in individual studies [21, 23, 29], whereas MMP-2, MMP-3, MMP-9, MMP-13, and cystatin C largely showed null results [21, 28, 29].

Overall, these exploratory findings suggest that certain markers—particularly SAA, IL-10, IL-11, neutrophil elastase, myeloperoxidase, pro-MMP-10, and endostatin—may hold promise for refining risk stratification after IVT, while others appear less informative.

Previous studies have consistently demonstrated the prognostic relevance of inflammatory biomarkers in ischemic stroke populations. Earlier systematic reviews and meta-analyses identified elevated CRP and IL-6 levels as significant predictors of unfavorable functional outcome and mortality after stroke [63–65]. More recent investigations have also supported the clinical utility of combined inflammatory biomarker assessment in stroke prognosis [66–68]. However, many prior studies evaluated biomarker levels at heterogeneous sampling time points during the acute and subacute phases of stroke. In contrast, the present meta-analysis exclusively included studies assessing baseline inflammatory biomarker levels obtained prior to thrombolytic treatment, thereby providing a more standardized evaluation of the prognostic relevance of pre-treatment inflammatory status.

In MT cohorts, CRP was the most frequently studied biomarker. Elevated CRP was often associated with worse functional outcome and mortality, although some studies reported neutral results after adjustment, indicating uncertain incremental prognostic value beyond established clinical predictors [39–45, 47, 48]. This indicates that while CRP reflects systemic inflammation, its prognostic value beyond established predictors remains uncertain. SAA has also been investigated, with higher concentrations associated with disability, while its link to mortality was not statistically significant.

Other inflammatory mediators have been assessed only sporadically. IL-6 and procalcitonin (PCT) were assessed in relation to poor outcomes, but no quantitative effect was demonstrated [41, 44, 45]. Chemokines such as MCP-1 showed no clear associations [41]. Markers of vascular inflammation and tissue remodeling were less consistently linked to outcome. Matrix metalloproteinase-9 (MMP-9) was studied in a small cohort, but no quantitative effect was demonstrated regarding poor outcome [44]. Similarly, vascular endothelial growth factor (VEGF) showed only a weak, nonsignificant trend toward worse outcomes [46].

The MT evidence was too fragmented to support quantitative synthesis. Although CRP was assessed in several studies, reported endpoints varied substantially, including poor functional

outcome using different mRS thresholds, mortality, hemorrhagic transformation, and symptomatic intracerebral hemorrhage. Follow-up time points also differed, ranging from early post-procedural outcomes to 3-month or 90-day assessments. For most other biomarkers, including IL-6, SAA, PCT, MCP-1, MMP-9, and VEGF, evidence was limited to one or two studies. In addition, MT cohorts differed in the proportion of patients receiving bridging IVT and in adjustment for key prognostic factors. Therefore, the currently available MT literature allows only descriptive interpretation, and biomarker-specific pooled estimates would not be methodologically reliable. Overall, CRP remains the most consistently studied inflammatory marker after MT, but its independent prognostic value remains uncertain. Evidence for other biomarkers is sparse and inconclusive.

Given the increasing role of MT in contemporary AIS management, recent studies have increasingly focused on the prognostic value of inflammatory and hemostatic biomarkers specifically in thrombectomy-treated cohorts. Recent systematic reviews and meta-analyses have demonstrated the potential predictive relevance of biomarkers such as CRP/albumin ratio and D-dimer for post-thrombectomy outcomes and complications [69, 70]. Furthermore, a meta-analysis from our group demonstrated that an elevated pre-treatment neutrophil-to-lymphocyte ratio (NLR) was consistently associated with poor functional outcome and increased mortality following reperfusion therapy, particularly in patients treated with MT [71]. A recent systematic review also highlighted the growing interest and potential clinical utility of biomarker-based prognostic stratification in MT cohorts [72]. These findings further support the clinical relevance of inflammatory biomarker assessment in modern reperfusion-treated stroke patients.

Importantly, pre-treatment inflammatory biomarkers may have a different biological meaning in MT cohorts, where large vessel occlusion—especially middle cerebral artery (MCA) occlusion—can induce a cytokine-driven inflammatory cascade with glial activation, pro-inflammatory cytokine and leukocyte release, and blood–brain-barrier disruption [73]. In MT-treated patients, this response is further shaped

by neutrophil activation, elevated fibrinogen, higher admission National Institutes of Health Stroke Scale (NIHSS) score, reperfusion-related leukocyte-endothelial adhesion, and microvascular obstruction after reperfusion [74]. Because collateral-dependent blood flow strongly determines infarct growth after large vessel occlusion, poor collaterals may result in more extensive tissue injury and a more pronounced inflammatory response [75]. Consequently, biomarkers in MT studies may reflect collateral failure, infarct expansion, and thromboinflammatory reperfusion injury more than a treatment-specific predictive signal comparable to IVT.

In conclusion, larger, prospective studies using standardized biomarker assessment, uniform outcome definitions, and consistent adjustment for MT-specific prognostic factors are needed to clarify their role in the thrombectomy setting.

LIMITATIONS

Several limitations of this systematic review and meta-analysis should be acknowledged. Although 37 studies were included in the systematic review, the number of studies available for quantitative synthesis was only 10. Only four biomarkers—C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and osteopontin—were included in the meta-analysis, and all pooled estimates were derived from cohorts treated with IVT. Data from patients undergoing MT were insufficient and too heterogeneous for quantitative pooling, limiting the generalizability of the meta-analytic findings across all reperfusion therapies.

Substantial clinical and methodological heterogeneity was present across the included studies. Most studies were observational and varied considerably in terms of patient populations, sample size, stroke severity, reperfusion modality, biomarker assay methodology, timing of blood sampling, covariate adjustment strategies, biomarker scaling, and definitions of poor functional outcome. Although random-effects models were used to account for between-study variability, they cannot fully overcome heterogeneity in

exposure measurement, model specification, and outcome definition. Therefore, pooled estimates should be interpreted as approximate summaries of association rather than definitive estimates of prognostic effect. Because only two to six studies were available for each pooled biomarker, formal subgroup analyses, sensitivity analyses, and meta-regression were not feasible.

The pooled estimates were based on study-level odds ratios reported in the original publications. No additional adjustment or recalculation from raw data was possible. Adjustment strategies differed across studies, and key prognostic variables such as age, baseline stroke severity, recanalization status, comorbidities, and renal function were not uniformly accounted for. Residual confounding therefore cannot be excluded.

Another important limitation is that biomarker effects were not reported on a uniform scale across studies. Some studies analyzed biomarkers as continuous variables, whereas others used log-transformed values or categorical cutoff thresholds. Cutoff values for inflammatory markers were inconsistent or absent in most studies, and individual participant data were not available to standardize effect estimates across a common biomarker scale. This limits the direct comparability of pooled odds ratios.

Although pre-treatment blood sampling was required for inclusion, exact sampling windows and assay methodologies were not consistently reported across studies. This may have introduced additional methodological heterogeneity. Potential publication bias cannot be fully excluded. Formal statistical tests for funnel plot asymmetry were not feasible because of the small number of studies per biomarker, and only CRP had enough studies to allow visual funnel plot assessment. In addition, the limited number of studies reporting secondary outcomes such as mortality and hemorrhagic transformation precluded quantitative synthesis for these clinically relevant endpoints.

Together, these limitations indicate that the results should be interpreted cautiously and highlight the need for larger, standardized, prospective studies using harmonized biomarker assays, consistent sampling time points, uniform

outcome definitions, and prespecified adjustment strategies.

CONCLUSIONS

In conclusion, this systematic review and meta-analysis underscores the prognostic potential of selected inflammatory biomarkers in patients undergoing IVT. IL-6 emerged as the most promising prognostic biomarker of poor functional outcome, whereas CRP proved unreliable and TNF- α showed borderline effects. Osteopontin may represent a promising but preliminary candidate biomarker, although current evidence is limited. Integration of inflammatory biomarkers with imaging and clinical data could improve risk stratification, inform individualized post-acute management—including follow-up strategies and therapeutic decision-making—and potentially facilitate the development of targeted anti-inflammatory therapies in reperfusion-treated AIS. Evidence in patients undergoing MT remains insufficient and too heterogeneous for quantitative conclusions. Larger standardized prospective studies are needed to determine whether inflammatory biomarkers add prognostic value beyond established clinical and imaging predictors across different reperfusion treatment pathways.

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Data Availability. All data analyzed in this study were obtained from previously published sources and are presented within the tables of this manuscript.

Declarations

Conflict of Interest. István Szegedi, Zsolt Barnabás Éles, Attila Nagy, and Zsuzsa Bagoly declare no conflict of interest.

Ethical Approval. This article is based exclusively on previously published research and does not involve any new data collection from human participants or animals conducted by the authors.

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