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Association between C-reactive protein and albumin and thrombolysis outcomes in stroke patients: A systematic review and meta-analysis

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Abstract

Background— Biomarkers such as albumin and C-reactive protein (CRP) have been investigated for their potential prognostic value following intravenous thrombolysis (IVT) in acute ischemic stroke (AIS).

Methods— Four databases (Web of Science, PubMed, Embase, Scopus) were searched for studies assessing albumin, CRP or high-sensitivity CRP (hs-CRP) levels in AIS patients receiving IVT. Risk of bias was assessed using New Castle Ottawa scale. Data were analyzed using random effects models with standardized mean differences (SMD) and odds ratios (OR) as appropriate.

Results— Twenty-six studies were included, all with low risk of bias. High baseline CRP (>5mg/dl) was associated with unfavorable functional recovery (modified Rankin Scale [mRS 3-6]) at 3 months (OR 1.72; 95% CI 1.17-2.52, p<0.01). Hs-CRP levels were significantly higher in patients with mRS 3-6 vs mRS 0-2 (MD 0.57; 95% CI [0.29, 0.86], p<0.01). However, CRP levels were not associated with HT (SMD 0.80; CI [-0.31: 1.90], p=0.16) or Mortality (SMD 0.39; CI [-0.07: 0.84], p=0.10). Patients who experienced HT had a significantly lower serum albumin at baseline compared with patients without HT (SMD -0.68; 95% CI [-1.04, -0.33], p<0.01). However, serum albumin level was not associated with functional recovery (SMD -0.21; CI [-0.56: 0.14], p=0.25).

Conclusion— This study highlights the potential of CRP and albumin as prognostic biomarkers in AIS patients undergoing IVT. Elevated CRP levels are associated with unfavorable functional outcomes, while low serum albumin levels carry a higher risk of hemorrhagic transformation. Incorporating these biomarkers into clinical practice could enhance risk stratification and guide post-treatment care.

Keywords— Serum albumin; stroke; hemorrhagic transformation; intravenous thrombolysis; C-reactive protein; CRP; hsCRP.

INTRODUCTION

Stroke remains a prevalent condition with prognosis and treatment outcomes influenced by factors such as clot characteristics (size and location) and patient-specific variables, including age and comorbidities.[1,2] Recent literature highlighted the importance of biomarkers such as C-reactive protein (CRP) levels reflecting systemic inflammation, and albumin levels reflecting nutritional status in predicting the prognosis.[3,4] Additionally, the value of albumin might be limited but CRP has emerged as a pivotal biomarker in

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predicting adverse outcomes across various clinical scenarios, including infections, chronic diseases such as cardiovascular and renal conditions, as well as monitoring treatment response and recurrence in cancer patients.[5]

Elevated CRP levels are observed in about 70% of stroke patients reflecting the systemic inflammatory response induced by the stroke, or the extent of tissue damage.[6-8] While the precise mechanisms linking high CRP levels to poor outcomes remain unclear, some studies suggest it may influence the coagulation process.[9] Albumin, although not directly affected by stroke itself, serves as a marker of frailty and morbidity. Lower albumin levels are associated with poor functional outcomes in stroke patients, likely due to albumin's neuroprotective properties, such as reducing infarct volume and perilesional edema.[10,11] However, attempts to correct albumin levels have not demonstrated clear benefits in improving stroke outcomes.[12]

In the context of specific stroke treatments, such as mechanical thrombectomy (MT) and intravenous thrombolysis (IVT), CRP and albumin have shown varying predictive roles.[13,14] A meta-analysis done by by Geravis de Liyis et al. demonstrated that elevated CRP levels in patients undergoing MT were associated with unfavorable outcomes, increased mortality, and complications, although albumin levels showed no significant correlation.[15] Among IVT-treated patients, several studies revealed that elevated CRP levels were linked to poor outcomes and higher mortality risk, while lower albumin levels were associated with an increased risk of hemorrhagic complications.[16,17] We sought to conduct a comprehensive review of the literature to evaluate the utility of CRP and albumin as associative biomarkers for clinical outcomes in stroke patients treated with IVT.

METHODS

Study design and search strategy

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The protocol of this study is not registered.

To identify relevant research, the AutoLit platform (Nested Knowledge, St. Paul, Minnesota, USA) was utilized to conduct a systematic literature search, eliminate duplicates, and access full-text publications. From inception up until June 2024, we searched four databases—PubMed, Scopus, Embase, and Web of Science—using a mix of keywords and Medical Subject Headings (MeSH) terms to find published literature regarding association of CRP, hs-CRP, albumin and AIS outcomes using search terms (“acute ischemic stroke”) AND (“CRP” OR “acute phase reactants” OR “Albumin”) AND (“thrombolysis”). In addition, we looked through the reference lists of the studies that were included in the search to identify relevant publications. A full search strategy in PubMed is presented in the supplementary materials.

Study selection

Two authors (SBJ and MF) worked separately to perform an initial literature screening that focused entirely on abstracts and titles. Thereafter, duplicate articles were removed. The same two authors separately conducted a thorough full-text screening to evaluate the research based on predefined inclusion and exclusion criteria. By consulting with a third author (AR), we meticulously rectified any discrepancies or disputes that arose along this procedure. We included (a) human studies, in which (b) baseline CRP, highly sensitive CRP (hsCRP), albumin or CAR was evaluated in (c) patients with AIS treated by thrombolysis. There were no restrictions regarding the date, or country of relevant investigations. Conversely, studies were not considered for inclusion in our analysis if they met the following criteria: (a) AIS treated by MT or no specification of treatment method; (b) no report of outcomes of interest; (c) case reports or case series with fewer than ten patients in total; (d) not published in English; and (e) conference abstracts, reviews, meta-analyses, letters and editorials

Data extraction

For every paper, two authors (SBJ, KE) retrieved basic identifying details such as the first author's last name, country of publishing, year of publication. Baseline characteristics, including sample size, study design, gender, age, baseline modified Rankin Scale (mRS), stroke severity based on NIHSS, infarct volume, presence of comorbidities, and follow-up duration were also collected. When two authors disagreed on how to fill out the standardized forms for data extraction, the third author (AR) settled the dispute.

Definitions of outcomes and complications

The goal of this meta-analysis was to determine the association between the aforementioned serum parameters and the following outcomes: (a) favorable functional recovery at 3 months follow up defined as modified Rankin Scale grades 0-2; 2) hemorrhagic transformation (HT) and symptomatic HT; 3) mortality at 3 months.

Risk of bias and quality of evidence assessment

All included studies were assessed for quality and possible bias using the Newcastle-Ottawa Scale (NOS).[19] Two independent reviewers assessed the quality of studies (SBJ and KE). A low risk of bias was indicated by a NOS score more than 7, a moderate risk of bias by a score between 5 and 7, and a high risk of bias by a score lower than 5. Selection (representativeness and sample size), comparability (absence of result at start of study, missing data or information, confounding variables), and outcome (assessment of outcome and sufficient follow-up period) are the three areas where the NOS assesses the possibility of bias. Sufficient duration of follow-up period was defined as ≥3 months.

Statistical analysis

Meta-analyses were conducted using R software version 4.3.2 (R Project for Statistical Computing) meta package version 6.5–0 and metafor package version 4.4–0. For dichotomous variables, we calculated Odds Ratios (ORs) and their corresponding 95% confidence intervals (CI) using a random-effects model. For continuous variables, we calculated the standardized mean difference (SMD) between groups using Hedge’s g as effect size with a 95% CI using a random effects-model. Data conversion was

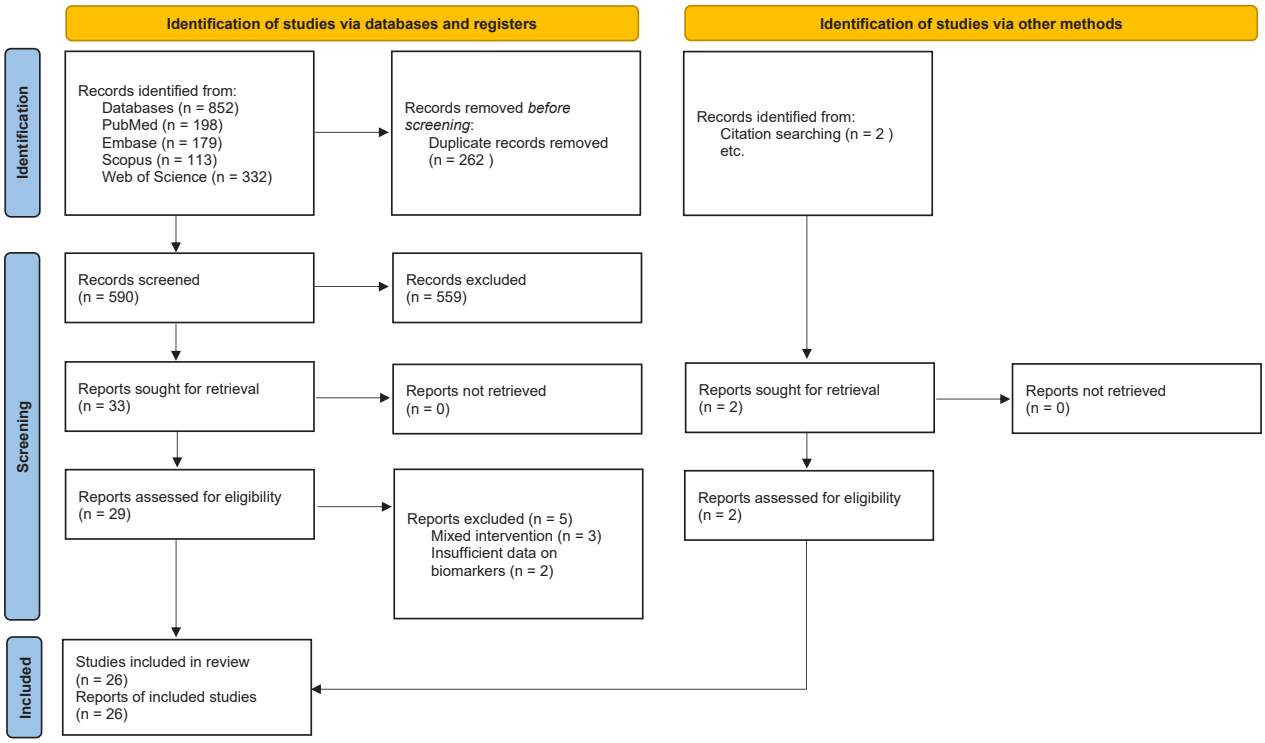


FIGURE 1: PRISMA flowchart of study selection.

done if necessary to calculate means and standard deviation from other data frames (e.g. median and quartiles), using DECoMA tool [20] We used Cochrane Q test p-values and I^2 statistics to evaluate heterogeneity; when either the p-value was less than 0.05 or the I^2 exceeded 50%, we regarded the heterogeneity to be significant. In case of high heterogeneity, we performed a sensitivity analysis to bring heterogeneity to an insignificant level. We performed influence analysis to find outliers. In case of finding only one outlier we performed a one-leave-out analysis to see the effect of outliers on overall outcome. In case that there were more outliers we performed a sensitivity analysis with removing outliers to bring the heterogeneity to an insignificant level.[21] Given that fewer than 10 studies were included in the analysis, it was not possible to conduct the Egger's test for publication bias or to perform a meta-regression.[22] Shiny app was used to create PRISMA flowchart.[23]

RESULTS

Study selection

The search identified 852 articles: 332 from Web of Science, 198 form PubMed, 179 from Embase and 113 from Scopus. Two additional references were found through handsearching the reference list of full texts included. After duplicate removal, 590 remaining titles were screened **(Fig. 1)**. Five studies were excluded after full text review: three due to mixed intervention (mechanical thrombectomy and IVT)[50-52] and two due to insufficient data on CRP levels.[53,54] Finally, 26 studies met the eligibility criteria[24-49] Hemorrhagic transformation was assessed in 9 studies (supplemental eTable 1), functional independence was assessed in 14 studies (supplemental eTable 2), mortality was assessed in 6 studies (supplemental eTable 3), and three studies assessed more than one outcome.

Risk of Bias

All studies scored ≥7 on quality assessment, showing low risk of bias. The quality assessment showed area of quality improvement in blinded assessment of studies. Most studies had significant differences in age and other confounders between studied groups, however this was addressed by performing adjusted analysis in most cases. Detailed quality assessment can be found in supplementary materials (supplemental eTable 4).

1. Meta-analysis

1.1 Albumin and Hemorrhagic Transformation

Five studies with 2,258 patients evaluated albumin levels among patients with (n=271) and without (n=1987) HT. Serum albumin levels were significantly lower in patients who experienced HT (SMD -0.68; 95%CI [-1.04: -0.33], P<0.01). However, high heterogeneity was observed (I^2= 85%, p<0.01) **(Fig. 2)**. One-leave-out analysis showed robustness of outcome after removing one outlier (Zhong, 2021) presented in online supplemental materials (SMD -0.53; 95%CI [-0.74: -0.32], P<0.001) **(Fig. S1)**.

1.2 Albumin and Functional independence

Three studies with 705 patients evaluated albumin levels between patients with favorable outcomes (mRS 0-2) (n=236) versus those with unfavorable outcome (mRS 3-6) (n=469). The analysis found no significant difference in albumin levels among groups with different functional status (SMD -0.21; CI [-0.56: 0.14], p=0.25) (I^2= 79%, p<0.01). The heterogeneity was high (I^2=79%, p < 0.01) **(Fig. 3)**. One-leave-out analysis showed robustness of outcome after removing one outlier (Yang, 2022) (SMD 0.21; 95%CI [-0.15: 0.56], P<0.001) presented in online supplemental materials. **(Fig. S2)**

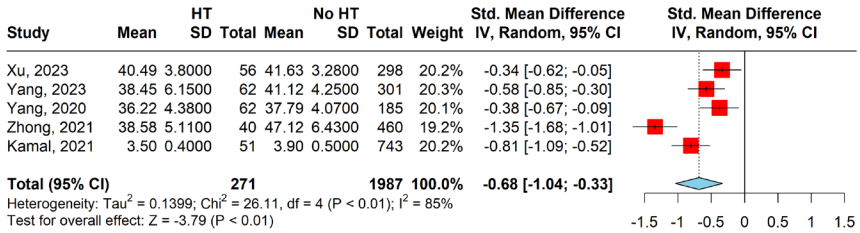


FIGURE 2: Association of baseline albumin level and hemorrhagic transformation (HT). Pooled analysis of five studies (n=2,258) showed significantly lower albumin in patients with HT (n=271) vs. without HT (n=1,987) (SMD -0.68; 95% CI: -1.04 to -0.33; p<0.01; I²=85%, p<0.01)

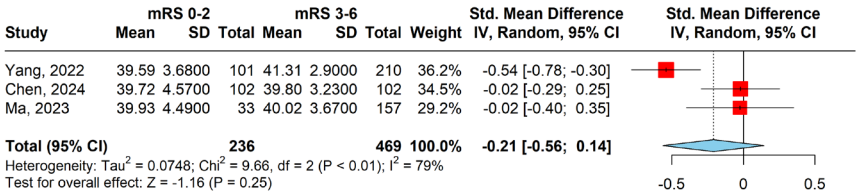
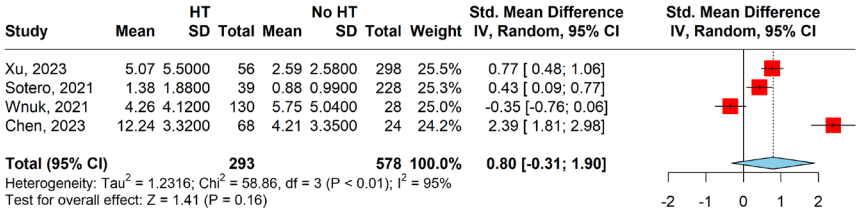


FIGURE 3: Association of baseline albumin level and functional independence. Meta-analysis of three studies (n=705) comparing patients with favorable (mRS 0–2, n=236) vs. unfavorable (mRS 3–6, n=469) outcomes showed no significant difference in albumin levels (SMD -0.21; 95% CI: -0.56 to 0.14; p=0.25; I²=79%, p<0.01)

4a



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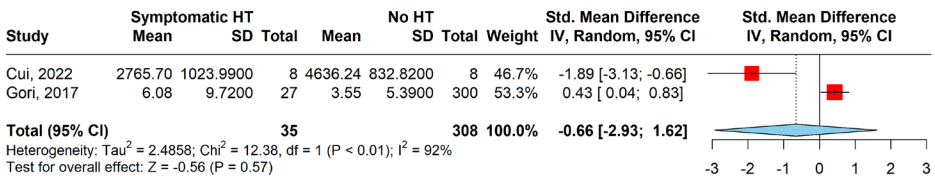
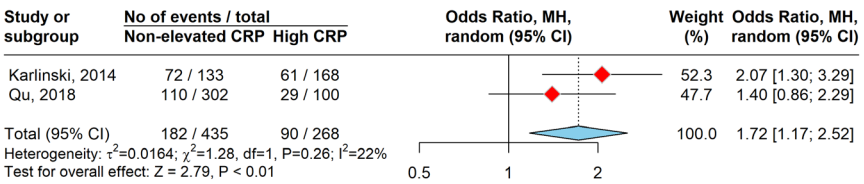


FIGURE 4: Association of baseline CRP levels and hemorrhagic transformation (HT) (A) and symptomatic HT (B)
a. Meta-analysis of four studies (n=871) showed no significant difference in CRP levels between patients with (n=293) and without (n=578) HT (SMD 0.80; 95% CI: -0.31 to 1.90; p=0.16; I²=95%, p<0.01)
b. Two studies evaluating symptomatic HT found no association with baseline CRP (SMD -0.66; 95% CI: -2.93 to 1.62; p=0.57; I²=92%, p<0.01)

5a



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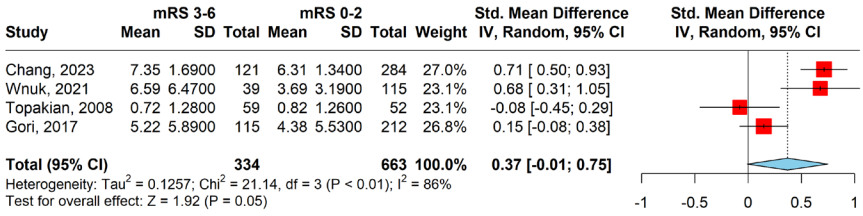

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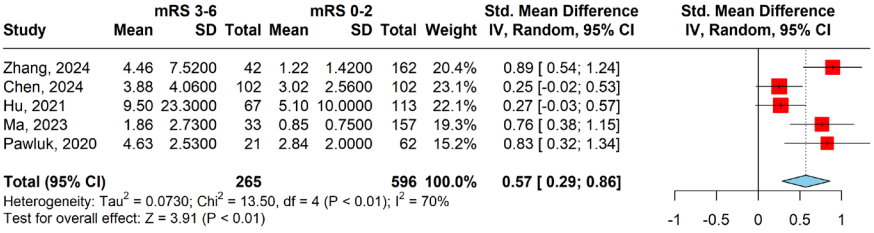

FIGURE 5: Association between baseline CRP and hs-CRP levels and functional outcomes

a. Association of CRP levels and functional dependence. Two studies (n=703) assessed odds of functional dependence (mRS 3–6) in patients with high (>5 mg/dL, n=268) vs. low (≤5 mg/dL, n=435) baseline CRP. High CRP was associated with greater odds of unfavorable outcomes (mRS 3-6) (OR 1.72; 95% CI: 1.17–2.52; p<0.01; I²=22%, p=0.26)

b. Association of baseline CRP levels and functional independence. Four studies (n=997) showed higher baseline CRP in patients with unfavorable outcomes (mRS 3–6, n=663) vs. favorable (mRS 0–2, n=334), but the difference was not statistically significant (SMD 0.37; 95% CI: -0.01 to 0.75; p=0.05; I²=86%, p<0.01)

c. Association of baseline hs-CRP levels and functional independence. Five studies found significantly higher baseline hs-CRP in patients with unfavorable outcomes at 3 months (MD 0.57; 95% CI: 0.29 to 0.86; p<0.01; I²=70%, p<0.01)

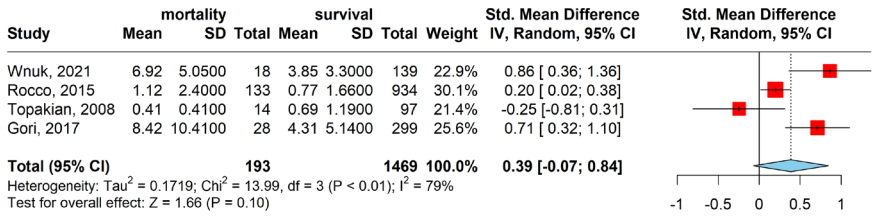

FIGURE 6: Association of baseline CRP and mortality

Four studies (n=1,662) compared CRP levels in patients who died (n=193) vs. survived (n=1,469) at 90-day follow-up. No significant difference was observed (SMD 0.39; 95% CI: -0.07 to 0.84; p=0.10; I²=79%, p<0.01)

2. C-reactive protein

2.1 CRP and Hemorrhagic Transformation

Four studies with 871 patients evaluated CRP levels among patients with (n=293) and without (n=578) HT. CRP level at baseline was not significantly associated with HT (SMD 0.80; CI [-0.31: 1.90], p=0.16). However, the heterogeneity was significant (I^2=95%, p<0.01) **(Fig. 4a)**. The influence analysis found no outliers between studies and leave-one-out analysis showed no influential effects for any single studies **(Fig. S3)**. In two studies, CRP level was assessed among patients with and without symptomatic HT. Pooling of these studies also showed no difference among groups, again with high heterogeneity (SMD -0.66; CI [-2.93: 1.62], p=0.57, I^2=92%, p<0.01) **(Fig. 4b)**. Due to low number of studies, a sensitivity analysis was not performed.

2.2 CRP and Functional Independence

Two studies assessed functional dependence (mRS 3-6) among patients with high (>5mg/dl) vs low CRP. In total 703 patients were evaluated including 435 patients with non-elevated CRP and 268 patients with high CRP. The pooled analysis showed that patients with high CRP had odds of experiencing unfavorable functional outcomes (mRS 3-6) (OR 1.72, 95% CI 1.17-2.52, p<0.01). There was low heterogeneity among studies (I^2=22%, p=0.26) **(Fig. 5a)**

Four studies with 997 patients evaluated CRP levels between patients with favorable outcomes (n=334) versus those with unfavorable outcome (n=663). The baseline CRP level was higher among patients with unfavorable outcomes but did not reach statistical significance and the heterogeneity was high (SMD 0.37; CI [-0.01: 0.75], p=0.05), (I^2= 86%, p<0.01) **(Fig. 5b)**. The influence analysis found no outliers between studies and leave-one-out analysis showed no influential effects for any single studies **(Fig. S4)**.

Five studies evaluated hs-CRP association with unfavorable outcomes at 3 months, and analysis revealed significantly higher levels of hs-CRP in patients with unfavorable outcomes (MD 0.57; CI [0.29: 0.86], p<0.01). Notably, there was significant heterogeneity (I^2= 70%, p<0.01) (Fig. 5c). No outliers were found and leave-one-out analysis showed no influential effects for any single studies **(Fig. S5)**.

2.3 CRP and Mortality

Four studies with 1,662 patients evaluated CRP levels between patients who died (n=193) and patients who survived (n=1469) at 90 days follow up. The CRP levels were comparable between groups (SMD 0.39; CI [-0.07: 0.84], p=0.10) with high heterogeneity levels (I^2= 79%, p<0.01) **(Fig. 6)**. Leave-one-out analysis showed no outliers on the association between baseline CRP and post-thrombolysis mortality **(Fig. S6)**.

DISCUSSION

This systematic review and meta-analysis aimed at investigating the association between thrombolysis outcomes in AIS patients and their albumin, and CRP levels. Our analysis showed that having elevated CRP and hsCRP levels might be associated with unfavorable functional outcomes in AIS patients. However, albumin levels were not associated with functional independence. Serum albumin levels were significantly lower in patients with HT after thrombolysis administration, while no significant differences in rates of HT were noted with CRP levels. CRP levels were also comparable between dead patients and survivors at 90 days after thrombolysis administration.

Previous studies have suggested that various factors, such as large cerebral infarction, the size of the infarction, atrial fibrillation, a higher NIHSS score, and hyperglycemia, can elevate the risk of intracranial hemorrhage (ICH) after rt-PA administration.[55-61] Elevated globulin levels have been identified as an independent risk factor for ICH following a stroke, likely due to their involvement in the inflammatory response, including inflammatory cytokines and acute-phase reactants produced by the liver.[62-65] Serum albumin is commonly used to assess nutritional status, and Aptaker et al.[66] proposed that serum albumin levels may be associated with the frequency of medical complications. Our analysis revealed that patients who experienced HT after thrombolysis had significantly lower serum albumin levels compared to those who did not experience HT. Post-stroke HT mainly occurs when blood-brain barrier permeability increases after vessel reperfusion, a process linked to proteolysis, oxidative stress, and leukocyte infiltration, particularly in the absence of rt-PA or surgery. This leads to further BBB rupture, which damages the neurovascular unit, including the extracellular matrix, endothelial cells, astrocytes, and neurons. Serum albumin, acting as a specific inhibitor of endothelial cell apoptosis and a key antioxidant, helps protect against both endogenous and exogenous oxidation. By strongly binding to copper ions, albumin inhibits copper ion-dependent lipid peroxidation at the cell membrane. Additionally, albumin is involved in transporting fatty acids to the post-stroke brain.[67-71] Due to its neuroprotective properties, individuals with normal albumin levels have a reduced incidence of HT.

Our findings suggest that elevated levels of CRP and hsCRP are associated with unfavorable functional outcomes in AIS patients. This observation is consistent with existing literature, which links systemic inflammation, as indicated by increased CRP levels, with poorer recovery and worse functional prognosis following stroke.[8,13,72-74] CRP is widely recognized as a marker of inflammation, and its elevation is thought to reflect ongoing inflammatory processes that may exacerbate neuronal injury and hinder recovery post-stroke. Elevated CRP levels have been associated with a pro-inflammatory state that could contribute to poor outcomes by promoting neurovascular damage, increasing the risk of secondary complications, and impairing tissue repair mechanisms.[75-77] Interestingly, despite the relationship between CRP and functional outcomes, we found no significant association between albumin levels and functional independence in AIS patients. This result contradicts some previous studies that have suggested a potential link between low albumin levels and poor functional outcomes. Albumin is often viewed as a marker of nutritional status and liver function, and lower albumin levels have been associated with worse outcomes

in various disease states, including stroke. However, our analysis suggests that the prognostic value of albumin may be limited when it comes to predicting functional recovery after thrombolysis. The lack of a significant association could reflect the complexity of stroke recovery, where other factors, including the extent of ischemic damage, early intervention, and rehabilitation, might play a more prominent role in determining functional outcomes than albumin alone.

Another key finding from our analysis was that serum albumin levels were significantly lower in patients with HT following thrombolysis. This observation aligns with the concept that hypoalbuminemia could be a potential risk factor for HT. Low albumin levels are known to be associated with a compromised blood-brain barrier and a higher propensity for bleeding, which may predispose patients to hemorrhagic complications after thrombolysis. However, it is important to note that this association was not observed with CRP levels. The absence of a relationship between CRP and HT in our analysis might suggest that the pathophysiological mechanisms underlying HT and inflammation are distinct. While elevated CRP levels may reflect general inflammation, it may not necessarily correlate with the specific inflammatory pathways involved in hemorrhagic transformation. Within our included studies, Xu et al.[37] investigated the association between the CRP-albumin ratio, and HT and found that patients with HT had a significantly higher ratio than others without HT after IVT administration. This, again, indicates that HT is probably associated with reduced albumin levels, not CRP and inflammation. Lastly, our analysis did not find any significant differences in CRP levels between deceased and surviving patients at 90 days post-thrombolysis. This finding suggests that while CRP may serve as a useful marker of early inflammatory responses following AIS, it may not be a strong predictor of long-term mortality. This is a notable observation, as CRP's role in acute stroke outcomes may be more relevant to short-term functional recovery rather than long-term survival, which could depend on a variety of other factors such as secondary stroke prevention, comorbid conditions, and post-stroke rehabilitation efforts.

While our study contributes to the understanding of predictors in thrombolysis outcomes, some limitations must be considered while interpreting the reported findings. The heterogeneity in the methodologies of the included studies, such as differences in timing of biomarker measurement and the use of various thrombolytic agents, may influence the generalizability of our findings. Besides, while CRP and albumin are important markers of inflammation and nutritional status, they represent only a subset of the complex network of biomarkers that may influence stroke outcomes. Future studies should consider investigating other inflammatory markers, as well as their interactions with genetic, clinical, and neuroimaging factors, to better predict outcomes and guide therapeutic interventions. Moreover, the impact of early inflammatory responses versus prolonged inflammation on long-term outcomes remains an area for further investigation, as acute-phase responses might differ in their prognostic significance compared to chronic inflammation.

CONCLUSION

Our meta-analysis suggests that elevated CRP and hsCRP levels are associated with worse functional outcomes in AIS patients after thrombolysis, while albumin levels do not have a significant association with functional independence. The lower albumin levels observed in patients with HT highlight the potential role of hypoalbuminemia in predicting thrombolytic complications. However, CRP levels did not show any association with hemorrhagic transformation or long-term mortality. These findings underline the importance of inflammatory markers in predicting outcomes after thrombolysis but also emphasize the need for further research to refine our understanding of the complex interplay between inflammation, stroke pathology, and recovery.

What is already known on this topic –

Biomarkers like CRP and albumin have been studied for their prognostic value in stroke outcomes.

What this study adds –

This study provides robust evidence from 26 high-quality studies regarding the predictive value of these biomarkers in IVT-treated AIS patients. This study highlights the association of elevated CRP with poor functional recovery and low albumin with a higher risk of hemorrhagic transformation.

How this study might affect research, practice or policy –

The findings reinforce the need to incorporate CRP and albumin measurements in routine stroke care for better outcome prediction and stimulates further research into optimizing therapeutic interventions based on biomarker profiles.

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SUPPLEMENTARY MATERIALS:

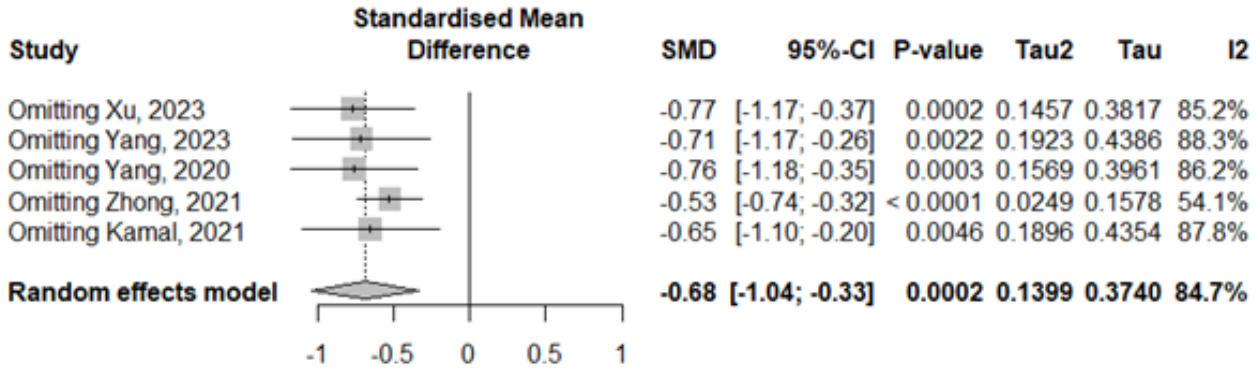

FIGURE S1: Leave-one-out analysis showing the effect of outliers (Zhong, 2021) on the association between baseline Albumin and post-thrombolysis hemorrhagic transformation

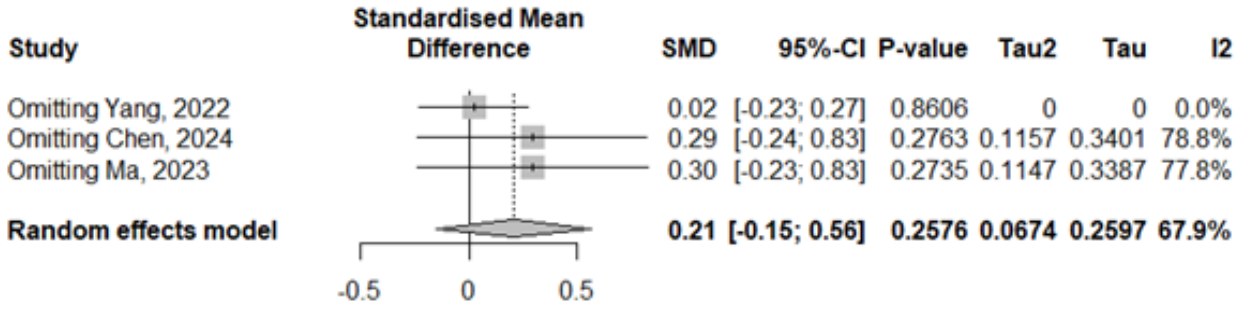

FIGURE S2: Leave-one-out analysis showing the effect of outliers (Yang, 2022) on the association between baseline Albumin and post-thrombolysis functional independence.

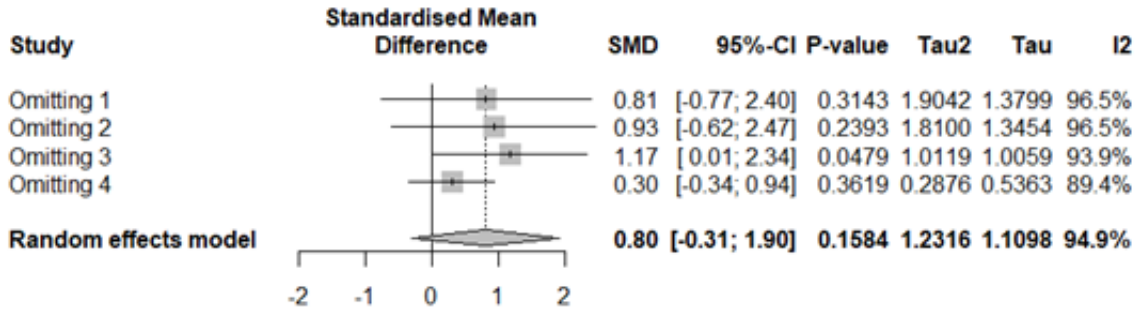

FIGURE S3: Leave-one-out analysis showing no outliers on the association between baseline CRP and post-thrombolysis hemorrhagic transformation.

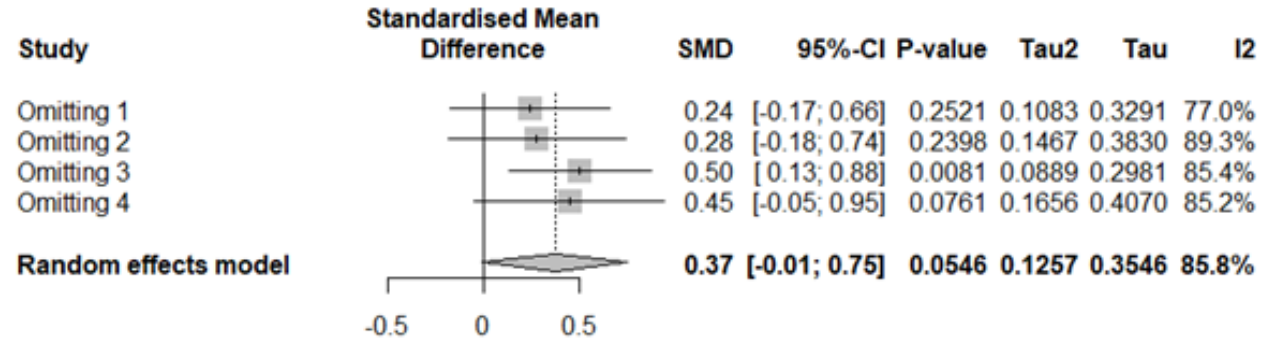

FIGURE S4: Leave-one-out analysis showing no outliers on the association between baseline CRP and post-thrombolysis functional recovery.

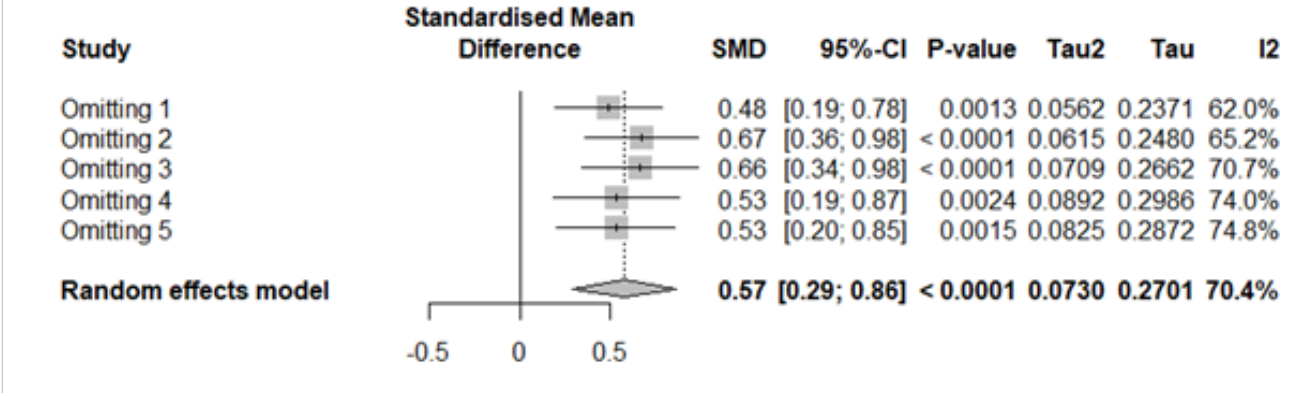

FIGURE S5: Leave-one-out analysis showing no outliers on the association between baseline hs-CRP and post-thrombolysis functional recovery.

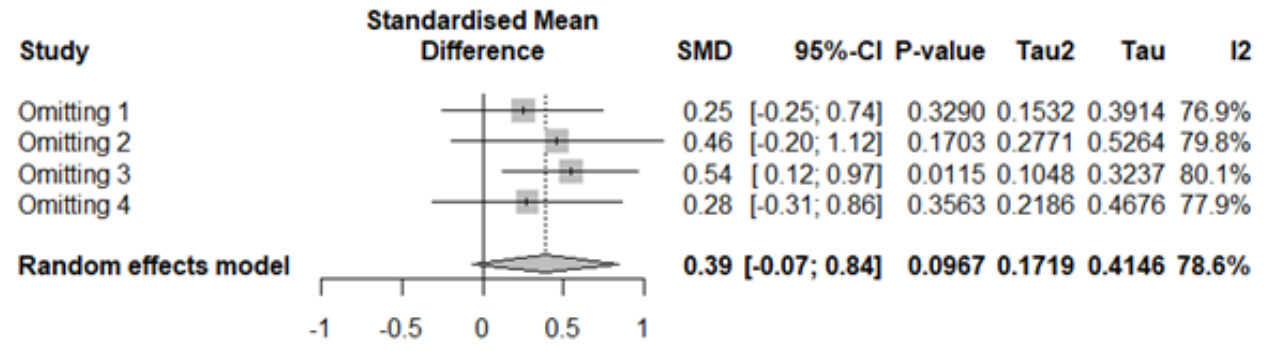

FIGURE S6: Leave-one-out analysis showing no outliers on the association between baseline CRP and post-thrombolysis mortality.

eTABLE 1: Demographic characteristics of studies that measured hemorrhagic transformation. *: These studies measured symptomatic intracranial hemorrhage (sICH).

Study, year	Country	Total, N	Age	Male, N (%)	NIHSS at admission	ASPECTS	HTN, group without HT, N (%)	HTN, group with HT, N (%)	DM, group without HT , N (%)	DM, group with HT, N (%)	Smoking, group without, N (%) HT	Smoking, group with HT, N (%)	Afib, group without HT, N (%)	Afib, group with HT, N (%)	Alcohol, group without HT, N (%)	Alcohol, group with HT, N (%)	HLP, group without HT, N (%)	HLP, group with HT, N (%)	Previous stroke, group without HT, N (%)	Previous stroke, group with HT, N (%)
Wnuk, 2021	Poland	158	The median age was 72 years (interquar-tile range 63–82)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Xu, 2023	China	354	The median age was 69 (range, 56 to 82 years)	232 (65.5%)	6 (range, 4 to 11)	-	228 (76.5)	44 (78.6)	93 (31.2)	18 (32.1)	94 (31.5)	8 (14.3)	68 (22.8)	32 (57.1)	-	-	-	-	-	-
Yang, 2020	China	247	63.20 ± 12.40	177(71.7)	12.0(9.0, 16.0)	-	122(65.9)	41(66.1)	40(21.6)	18(29.0)	79(42.7)	21(33.9)	48(25.9)	23(37.1)	55(29.9)	23(37.1)	20 (35.7)	141 (47.3)	8 (14.2)	47 (15.8)
Yang, 2023	China	363	65 (55–73)	237 (65.3)	7 (3–13)	14 (13–14)	210 (69.8)	39 (62.9)	72 (23.9)	14 (22.6)	125 (41.5)	21 (33.9)	85 (28.2)	29 (46.8)	54 (17.9)	10 (16.1)	31 (10.3)	7 (11.3)	41 (13.6)	9 (14.5)
Zhong, 2021	China	500	-	310 (62)	-	-	249	25	142	13	253	21	115	14	193	18	-	-	11/29	83/377
Gori, 2017	Italy	327	68.9 ± 12	190 (58.1)	1.9±6.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chen, 2023	China	92	-	58 (63)	-	-	48 (70.6)	14 (58.3)	24 (35.3)	4 (16.7)	-	-	-	-	-	-	-	-	22 (32.4)	6 (25.0)
Cui, 2022*	China	16	-	6 (37.5)	-	-	6 (75.0)	7 (87.5)	2 (25.0)	2 (25.0)	2 (25.0)	1 (12.5)	1 (12.5)	0	1 (12.5)	1 (12.5)	-	-	2 (25.0)	2 (25.0)
Kamal, 2021*	USA	794	-	409 (51.5)	-	-	-	-	161 (21.6%)	23 (45%)	-	-	78 (10.4%)	13 (25.4%)	-	-	-	-	-	-

HT: hemorrhagic transformation, N: number, NIHSS: National Institutes of Health Stroke Scale, ASPECTS: Alberta Stroke Program Early CT Score, HTN: Hypertension, DM: Diabetes mellitus, Afib: Atrial fibrillation, HLP: Hyperlipidemia.

eTABLE 2: Demographic characteristics of studies that measured mortality at 3 months.

Study, year	Country	Total, N	Age	Male, N (%)	NIHSS at admission	ASPECTS	HTN, group without mortality at 3 months, N (%)	HTN, group with mortality at 3 months, N (%)	DM, group without mortality at 3 months, N (%)	DM, group with mortality at 3 months, N (%)	Smoking, group without mortality at 3 months, N (%)	Smoking, group with mortality at 3 months, N (%)	Afib, group without mortality at 3 months, N (%)	Afib, group with mortality at 3 months, N (%)	Alcohol, group without mortality at 3 months, N (%)	Alcohol, group with mortality at 3 months, N (%)	HLP, group without mortality at 3 months, N (%)	HLP, group with mortality at 3 months, N (%)	Previous stroke, group without mortality at 3 months, N (%)	Previous stroke, group with mortality at 3 months, N (%)
Wnuk, 2021	Poland	158	The median age was 72 years (interquartile range 63–82)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Montaner, 2006	Spain	143	70.6+10.6	73 patients (51%)	17 (range, 5 to 23)	-	50,8	68,4	15,7	31,6	20,2	20	37,7	52,6	-	-	32	38,9	9,3	37,5
Topakian, 2008	Austria	111	68.9±12.2	54 (48.6)	14 (range 4–25)	-	74 (76)	9 (64)	20 (21)	2 (14)	20 (21)	5 (36)	28 (29)	7 (50)	-	-	28 (29)	4 (29)	18 (19)	1 (7)
Tang, 2022	China	979	66.8	63,60%	6.0 (3.0, 12.0)	-	608 (68.5)	68 (74.7)	212 (23.9)	23 (25.3)	400 (45.0)	39 (42.9)	-	-	276 (31.1)	31 (34.1)	107 (12.0)	14 (15.4)	-	-
Gori, 2017	Italy	327	68.9 ± 12	190 (58.1)	1.9±6.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rocco, 2015	Germany	1242	73 (65–80)	657 (53)	12 (7–17)	-	706 (75.6)	114 (87)	205 (21.9)	50 (39)	-	-	282 (30.2)	66 (51)	-	-	-	-	148 (15.8)	36 (28)

N: number, NIHSS: National Institutes of Health Stroke Scale, ASPECTS: Alberta Stroke Program Early CT Score, HTN: Hypertension, DM: Diabetes mellitus, Afib: Atrial fibrillation, HLP: Hyperlipidemia

eTABLE 3: Demographic characteristics of studies that measured mRS (modified Rankin Scale) at 3 months (studies with * measured mRS at discharge).

Study, year	Country	Total, N	Age	Male	NIHSS at admission	ASPECTS	HTN, group with mRS 0-2, N (%)	HTN, group with mRS>2, N (%)	DM, group with mRS 0-2, N (%)	DM, group with mRS>2, N (%)	Smoking, group with mRS 0-2, N (%)	Smoking, group with mRS>2, N (%)	Afib, group with mRS 0-2, N (%)	Afib, group with mRS>2, N (%)	Alcohol, group with mRS 0-2, N (%)	Alcohol, group with mRS>2, N (%)	HLP, group with mRS 0-2, N (%)	HLP, group with mRS>2, N (%)	Previous stroke, group with mRS 0-2, N (%)	Previous stroke, group with mRS>2, N (%)
Zhang, 2024	China	204	69.1±12.3	131 males (65.4%)	4.0 [2.0, 7.0]	-	115 (70.9)	32 (76.1)	61 (37.6)	24 (57.1)	35 (21.6)	7 (16.6	14 (8.6)	12 (28.5)	50 (30.8)	10 (23.8)	120 (74.1)	21 (50.0)	-	-
Chang, 2023	China	405	66.08 ± 8.11	181 (44.7)	6 (4–8)	10 (9–10)	216 (76.06)	91 (75.21)	141 (49.65)	52 (42.97)	113 (39.79)	44 (36.36)	35 (12.32)	18 (14.88)	87 (30.63)	36 (29.75)	-	-	-	-
Chen, 2024	China	204 (after match-ing)	75.00 [65.00, 83.00]	111 (54.4)	NIHSS score (0–4) 38 (18.6) NIHSS score (5–15) 132 (64.7) NHISS score (16–20) 26 (12.7) NIHSS score (21–42) 8 (3.9)	-	303 (68.2)	72 (70.6)	77 (75.5)	26 (25.5)	31 (30.4)	36 (35.3)	36 (35.3)	37 (36.3)	18 (17.6)	19 (18.6)	-	-	18 (17.6)	22 (21.6)
Hu, 2021	China	183	64.9 ± 10.5	123 (67.2)	4 (IQR 3-7)	-	71 (62.8)	52 (74.3)	15 (13.3)	26 (37.1)	42 (37.2)	20 (28.6)	12 (10.6)	17 (24.3)	-	-	-	-	25 (22.1)	29 (41.4)
Ma, 2023	China	190	70.389 ± 11.675	122 (64.2)	4.000 [3.000,6.000]	-	104 (66.2)	24 (72.7)	46 (29.3)	10 (30.3)	45 (28.7)	6 (18.2)	11 (7.0)	2 (6.1)	26 (16.6)	2 (6.1)	-	-	-	-
Pawluk, 2020	Poland	83	66 35 to 92median range	61,50%	-	-			22 (25.5)	13 (61.9)	-	-	6 (9.7)	5 (23.8)	-	-	24 (38.7)	10 (47.6)	-	-
Sotero, 2021	Portugal	267	median IQR 74 (64-82)	133 (49.8)	14 (8-19)	-	69 (71.1)	127 (74.7)	21 (21.6)	50 (29.4)	-	-	22 (22.7)	74 (43.5)	-	-	42 (43.3)	94 (55.3)	14 (14.4)	23 (13.5)
Wang, 2023	China	417	67.8± 3.2	239/417	4 (interquartile range, 2–10)	-	181(61.8)	91(73.4)	54(18.4)	33(26.6)	111(37.9)	35(28.2)	-	-	-	-	62 (21.2)	21 (16.9)	42 (14.4)	15 (12.1)
Wnuk, 2021*	Poland	158	The median age was 72 years (interquartile range 63–82)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Xu, 2023*	China	354	The median age was 69 (range, 56 to 82 years)	232 patients (65.5%) were men	6 (range, 4 to 11)	-	228 (76.5)	44 (78.6)	93 (31.2)	18 (32.1)	94 (31.5)	8 (14.3)	68 (22.8)	32 (57.1)	-	-	-	-	-	-
Yang, 2022	China	311	-	196 (63)	-	-	130 (61.90)	75 (74.26)	43 (20.48)	20 (19.80)	66 (31.43)	14 (13.86)	39 (18.57)	31 (30.69)	-	-	21 (10.00)	17 (16.83)	19 (9.05)	20 (19.80)
Rocco, 2015	Germany	1242	73 (65–80)	657 (53 %)	12 (7–17)	-	385 (73 %)	321 (80 %)	107 (20 %)	98 (25 %)	-	-	129 (25 %)	153 (38 %)	-	-	-	-	88 (17 %)	60 (15 %)
Topakian, 2008	Austria	111	68.9±12.2	54 (48.6)	14 (range 4–25)	-	74 (76)	9 (64)	20 (21)	2 (14)	20 (21)	5 (36)	28 (29)	7 (50)	-	-	28 (29)	4 (29)	18 (19)	1 (7)
Gori, 2017	Italy	327	68.9 ± 12	190 (58.1)	1.9±6.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

N: number, NIHSS: National Institutes of Health Stroke Scale, ASPECTS: Alberta Stroke Program Early CT Score, HTN: Hypertension, DM: Diabetes mellitus, Afib: Atrial fibrillation, HLP: Hyperlipidemia

eTABLE 4: Quality assessment of included studies based on Newcastle Ottawa Scale.

Quality questions	Zhang, 2024	Yang, 2022	Chang, 2023	Chen, 2024	Hu, 2021	Ma, 2023	Pawluk 2020	Sotero, 2021	Wang, 2023	Wnuk, 2021	Xu, 2023	Yang, 2020	Yang, 2023	Rocco, 2015	Montaner, 2006	Topakian, 2008	Zhong, 2021	Chen, 2023	Cui, 2022	Kamal, 2021	Tang, 2022	Gori, 2017	Cheng, 2023	Karlinski, 2014	Che, 2017	Qu, 2018
Q1	*	*	*	*	*	*	*	*	`*	*	*	*	*	*	*	*	*	*	*	*	*	`*	*	*	*	*
Q2	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Q3	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Q4	*	*	*	*	*	*	*	*	*	*	*	-		*	*	*	*	*	*	*	*	*	*	*	*	*
Q5	**	**	**	**	**	**	**	**	**	**	**	**	**	*	-	**	**	**	**	**	**	**	**	**	**	**
Q6	-	-	-	*	*	-	-	-	-	-	*	-	-	-	*	-	-	-	-	*	-	-	-	-	*	-
Q7	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Q8	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Score	8	8	8	9	9	8	8	8	7	8	9	7	7	7	7	8	8	8	8	9	8	8	8	8	9	8

Q1: Representativeness of the Exposed Cohort

Q2: Selection of the Non-Exposed Cohort

Q3: Ascertainment of Exposure

Q4: Demonstration That Outcome of Interest Was Not Present at Start of Study

Q5: Comparability of Cohorts on the Basis of the Design or Analysis

Q6:) Assessment of Outcome (blinded assessment of outcome)

Q7: Was Follow-Up Long Enough for Outcomes to Occur (3 months)

Q8: Adequacy of Follow Up of Cohorts (lost to follow up<20%)

Study	Inclusion criteria	Exclusion criteria
Xu, 2023	Any patient who received alteplase at 0.9 mg/kg until a maximum total dose of 90 mg within 4.5 h of stroke onset was included in the study unless (1) C-reactive protein and albumin levels at admission were unavailable, (2) Computed tomography was not performed within 36 h after intravenous thrombolysis, (3) Patients had an immune disorder or severe infection, defined as a history of cancer, hematologic disease, use of an immunosuppressant or the presence of sepsis on admission, (4) Low-dose alteplase was used, or (5) Thrombolysis was interrupted for reasons other than HT.	-
Zhang, 2024	(1) It met the diagnostic criteria set out in the "Guidelines for the diagnosis and treatment of acute ischemic stroke in China 2018".17 (2) It was the first onset, and the imaging diagnosis and laboratory diagnosis indicators at admission were consistent with indications of intravenous thrombolysis. (3) The onset time of symptoms was <4.5h. (4) The patients and their families agreed to be included in this study and follow-up.	(1) Patients with a history of malignant tumor and antitumor-related therapy; (2) Patients with a history of infection within the past 1 week and treated with anti-infection drugs; (3) Deaths during treatment; (4) The disease has a new cerebral hemorrhage.
Yang, 2022	Within 4.5 h of AIS onset, IVT r-tPA (0.9 mg/kg, maximum of 90 mg) was adopted for therapy with 10% of the total as a bolus and 90% by a 60-min infusion. The exclusion criteria were as follows: (1) Undergoing mechanical embolectomy followed by IVT; (2) With recent or concurrent infections; (3) With immunological disease; (4) With tumor; (5) With cirrhosis or renal failure; (6) Missing follow-up data.	Patients with recent or concurrent infections and/or with immunology disease and/or with tumor and/or with cirrhosis or renal failure and/or missing follow-up data.
Chang, 2023	All patients who had consecutive follow-ups following AIS diagnosis and administration using intravenous rt-PA in 4.5 h stroke onset or intravenous urokinase in 6 h stroke onset	(1) Were subjected to a bridging therapy made of intravenous thrombolysis and endovascular therapy; (2) Had missing baseline data, three-month mRS scores, and NIHISS scores; (3) Achieved a pre-stroke modified Rankin Scale (mRS) score >2; (4) Had a combination of other serious diseases, for instance, recently severe infections, severe liver and kidney diseases, auto-immunological diseases, hematological or rheumatic disorders, and malignant tumors; (5) Had an onset-to-treatment time (OTT) of more than 6 h; (6) Had no follow-up visit or missed visit. Finally, the study covered a total of 405 AIS patients.

Study	Inclusion criteria	Exclusion criteria
Chen, 2024	1. Diagnosis of AIS and received IVT therapy within 4.5 h after onset; 2. Age ≥18 years old.	1. Clinical data is not complete; 2. Diagnosed with stroke mimics; 3. Received endovascular treatment after IVT; 4. There are other serious internal medicine system diseases that coexist before stroke.
Hu, 2021	All patients were older than 18 years and received IVT within 4.5 h of symptom onset.	Patients who received endovascular therapy, diagnosis of stroke mimics, unclear time of symptom onset, autoimmune disease and patients with systemic infections within 2 weeks before stroke or during the first 24 h after IVT. Patients whose serum was not collected and those treated with steroids or lost to follow-up at 3 months were also excluded.
Ma, 2023	(1) Aged over 18 years old; (2) Diagnosed with AIS according to the Chinese AIS diagnosis and treatment guidelines; (3) Received rt-PA intravenous thrombolysis within 4.5 h of symptom onset [6]; (4) Premorbid mRS ≤ 2.	(1) Bridging therapy patients; (2) Patients with malignant tumors, autoimmune diseases, or blood system diseases; (3) Acute or chronic infections; (4) Severe hepatic or renal insufficiency; (5) Patients with missing follow-up data
Pawluk, 2020	Caucasian patients with AIS treated with IV-thrombolysis The data was gathered only from patients treated <4.5 h from stroke onset who gave a written informed consent.	Those with combination therapy (intravenous plus endovascular apy), concomitant myocardial infarction on the stroke onset and those who died within 24 hof stroke onset were excluded from the analysis. We have also excluded patients with prior history of stroke, chronic inflammatory and autoimmune diseases, neoplasms, steroid use and severe trauma or acute infections confirmed within ±3 days from hospital admission.
Sotero, 2021	Acute ischemic stroke treated with IV-tPA	Concomitant disorders lack of data related to functional outcome
Wang, 2023	Patients older than 18 years with ischemic stroke onset within 4.5h accepting IVT were included	Those with recurrent strokes with mRS ≥ 1, an acute infection preceding stroke, autoimmune diseases and chronic inflammatory diseases, severe hepatic, renal, cardiac or respiratory diseases and known malignancy or pregnancy were excluded. Additionally, patients with diagnosis of transient ischemic attack (TIA) based on completely revised of symptoms and no acute infarct on the MRI or follow-up CT scans; or who died at the ED or transferred to another hospital; or without complete data of WBC, CRP or RDW were excluded.

Study	Inclusion criteria	Exclusion criteria
Wnuk, 2021	All patients were of Caucasian origin and were treated with IVT	Excluded were patients with infection (n = 83) as described previously [13]. The lack of infection was determined by the exclusion of patients with fever, signs of infection in the physical examination, or those who needed antibiotics during subsequent hospitalization. Moreover, all patients underwent a routine chest x-ray, urine test and internal medicine consultation during the first 3 days since admission. Additionally, follow-up internal medicine consultation was performed in case of CRP elevation and before discharge. As the presence of malignant tumor was the exclusion criteria for IVT in AIS, there were no patients with this condition enrolled in our study.
Yang, 2020	Patients treated with IVT within 4.5 h of symptom onset	(1) Contraindications of IVT according to established guidelines, (2) Cdditional endovascular therapy (EVT).
Yang, 2023	Ischemic stroke patients who received intravenous thrombolysis with t-PA in our hospital from Jan 2017 to May 2022	(a) Diagnosed with stroke mimics; (b) Received endovascular treatment (including endovascular thrombectomy and arterial thrombolysis) after intravenous thrombolysis; (c) Had cancer, immunology, or acute infection diseases; and (d) Incomplete baseline clinical data.
Rocco, 2015	All patients admitted to our tertiary care hospital who underwent intravenous thrombolysis for acute ischemic stroke were included	-
Montaner, 2006	151 consecutive patients who had a documented middle cerebral artery (MCA) occlusion on transcranial Doppler ultrasonography (TCD) and received tPA	Four patients who had very high CRP levels (6 mg/dL) probably because of an infection before stroke were excluded from further analysis.
Topakian, 2008	Stroke patients undergoing IV thrombolysis	Individuals with stroke involving a territory other than the middle cerebral artery, those with known inflammatory or malignant diseases, and those probably infected (admission CRP >6mg/dl).

Study	Inclusion criteria	Exclusion criteria
Zhong, 2021	Five hundred patients with acute cerebral infarction who received IVT with alteplase within 4.5 h after the onset of disease (1) Aged 18 to 80 years; (2) Acute cerebral infarction onset time within 4.5 h; (3) Intracranial hemorrhage confirmed by CT scan and acute large area cerebral infarction demonstrated by imaging; and (4) Patients and patients' family members having signed the informed consent form.	(1) Patients with cerebral hemorrhage confirmed by CT scan with symptoms suggesting the presence of subarachnoid hemorrhage; (2) Patients who had previous history of brain arteriovenous malformation, intracranial tumor, brain aneurysm (ruptured or not ruptured); patients who had history of cerebral infarction, cerebral hemorrhage, traumatic brain injury or myocardial infarction except old lacunar infarct without symptoms of neurological deficit in the last 3 mo; patients with gastrointestinal hemorrhage or urinary hemorrhage in the last 3 mo; patients who underwent major surgery in the past 2 wk; patients who had vascular complications arising from hemostasis after arterial puncture; (3) Patients with severe heart, liver and kidney dysfunction; (4) Patients with active bleeding or trauma (fracture); (5) Patients with systolic pressure > 180 mmHg or diastolic pressure > 100 mmHg before thrombolysis; (6) Patients with platelet count below 100 × 109/L, blood glucose < 2.7 or > 22.2 mmol/L; (7) Patients who received heparin therapy with prolonged activated partial thromboplastin time (APTT) or orally took anticoagulants with international normalized ratio (INR) > 1.5; (8) Pregnant women; and (9) Patients who refused to cooperate with the study.
Chen, 2023	Acute onset; focal neurological deficits (one side of the face or limb weakness or numbness, language barriers, etc.), a small number of comprehensive neurological deficits; responsible lesions or symptoms/signs on imaging lasted for more than 24 hours;	Exclusion of non-vascular causes; brain CT/MRI excluded cerebral hemorrhage. Patients without bleeding;
Cui, 2022	Patients received a standard dose of rtPA (0.9 mg/kg, maximum 90mg; manufacturer: Boehringer Ingelheim) within 4.5 h after the symptoms onset.	(1) Patients received urokinase, (2) Patients received a non-standard dose of rtPA, (3) Patients received an endovascular intervention, (4) Patients lacked complete clinical data, and (5) Blood samples were not collected prior to intravenous thrombolysis.
Kamal, 2021	We studied all consecutive patients with AIS who were treated with IVT using intravenous recombinant tissue plasminogen activator (IV rtPA) with or without IAT	-

Study	Inclusion criteria	Exclusion criteria
Tang, 2022	Patients with acute ischemic stroke who underwent IVT	(1) Age < 18 years old; (2) Had incomplete followup; (3) Had no measurement of variables required to calculate the malnutrition risk during hospitalization; (4) Had a history of chronic lymphocytic leukemia, lymphoma, other malignant tumors, as well as active or chronic inflammatory disorders. We also excluded patients treated with endovascular treatment after IVT.
Cheng, 2023*	(1) Patients met the diagnostic criteria for AIS confirmed by head CT or MRI and complied with guidelines for early management of patients with acute ischemic stroke [10, 11]; (2) The time from onset to intravenous thrombolysis was less than 6 h; (3) National Institute of Health Stroke Scale (NIHSS) scores were obtained before and 24 h after thrombolysis;	Patients with other stroke etiologies (including infectious, immune, genetic, vascular, and drug use caused stroke) according the TOAST classification were excluded patients with neurological impairment due to intracranial tumours or craniocerebral trauma were excluded; patients received endovascular treatment were excluded; and studies with incomplete data (no pre-thrombolysis or post-thrombolysis NIHSS score; hs-CRP were not examined before thrombolysis) were excluded
Che, 2017	428 consecutive AIS patients receiving IV rt-PA within 4.5 h of symptom onset	-
Qu, 2018	AIS patients (>18 years of age) treated with intravenous rt-PA within 4.5 hours of onset	Patients with systemic infections within 2 weeks before stroke or during the first 24 hours after IVT(n=11), those with no WBC counts measurements (n=59) and those with no CRP measurements (n=34)