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Original Article

Effect of connective tissue growth factor and inflammatory factors on the condition and prognosis of patients undergoing reperfusion for acute ischemic stroke

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Abstract: Objective: To evaluate the impact of connective tissue growth factor (CTGF) and inflammatory factors on the condition and prognosis of patients undergoing reperfusion therapy for acute ischemic stroke (AIS). Methods: A retrospective analysis was conducted on 212 AIS patients who received reperfusion therapy at Wu Xi Traditional Chinese Medicine Hospital, Suqian Hospital of Traditional Chinese Medicine, The Affiliated Wuxi People's Hospital of Nanjing Medical University from January 2021 to January 2024. Patients were divided into a control group (modified Rankin Scale [mRS] score = 0-3, n = 132) and a study group (mRS score = 4-6, n = 80). The mRS and National Institutes of Health Stroke Scale (NIHSS) scores were compared between the two groups 90 days post-reperfusion. Levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and CTGF at the time of reperfusion were measured, and their correlations with the mRS and NIHSS scores were analyzed. Logistic regression was used to identify factors influencing patient prognosis. Results: The control group had significantly lower levels of IL-6, TNF-α, and CTGF at reperfusion compared to the study group (all $P < 0.050$). Ninety days post-reperfusion, the control group showed significantly lower mRS and NIHSS scores than the study group (both $P < 0.001$). Levels of IL-6, TNF-α, and CTGF at reperfusion were positively correlated with mRS and NIHSS scores 90 days post-reperfusion (all $P < 0.050$). Logistic regression analysis identified age, and IL-6, TNF-α, and CTGF levels at reperfusion, as independent factors influencing prognosis. Conclusion: In AIS patients undergoing reperfusion, higher levels of CTGF, IL-6, and TNF-α at reperfusion were associated with worse mRS and NIHSS scores 90 days later. Age and elevated levels of these markers were independent predictors of poorer prognosis.

Keywords: Connective tissue growth factor, inflammatory factors, acute ischemic stroke, reperfusion, prognosis

Introduction

Stroke is a leading cause of disability and death worldwide, with acute ischemic stroke (AIS) as one of its main subtypes [1]. In China, the aging population has made stroke the foremost cause of mortality and adult disability [2]. The formation of blood clots in cerebral blood vessels results in reduced blood flow and oxygen deprivation in brain tissues [3, 4]. This condition can cause sudden symptoms like facial asymmetry, speech difficulties, and limb weakness [3].

Emergency intervention of brain damage in AIS, and timely reperfusion therapy are essential for salvaging the ischemic penumbra [4]. Early reperfusion can improve outcomes but complicated by reperfusion injury, which occurs when the reestablished blood flow aggravates damage in previously ischemic tissues [5, 6]. The ischemic process itself also activates inflammation due to the release of inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These inflammatory factors can disrupt the blood-brain barrier, induce neuronal apoptosis, and

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worsen brain injury [7]. IL-6, in particular, not only promotes inflammation but also activates pathways, leading to an inflammatory cascade [8, 9].

Research suggests that connective tissue growth factor (CTGF), a member of the cell communication network family, plays a role in inflammation modulation and tissue repair [10, 11]. However, the combined effects of CTGF and inflammatory factors on the prognosis of AIS patients require further investigation.

This retrospective study analyzed the levels of CTGF, IL-6, and TNF-α in 212 AIS patients who received reperfusion therapy at Wu Xi Traditional Chinese Medicine Hospital. The study aimed to evaluate the impact of these factors on patient prognosis, providing insights for future therapeutic approaches for AIS.

Materials and methods

Sample information and grouping

Clinical data from 250 AIS patients who underwent reperfusion at Wu Xi Traditional Chinese Medicine Hospital, Suqian Hospital of Traditional Chinese Medicine, The Affiliated Wuxi People's Hospital of Nanjing Medical University between January 2021 and January 2024 were retrospectively collected and analyzed. The study was approved by the Medical Ethics Committee of Wu Xi Traditional Chinese Medicine Hospital. After applying strict inclusion and exclusion criteria, 212 patients were enrolled.

Inclusion criteria: (1) Diagnosis of AIS confirmed according to the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (2018 [2]). (2) Patients who received reperfusion therapy at Wu Xi Traditional Chinese Medicine Hospital. (3) Previous modified Rankin Scale (mRS) score ≤ 1 point [12]. (4) Complete clinical and follow-up data available. (5) Onset time within 24 hours and an initial NIHSS score between 6 and 25 [13].

Exclusion criteria: (1) Patients with cerebral infarction due to rare causes (e.g., arteritis, hematologic disorders, rheumatic immune diseases, aortic dissection, rheumatic heart disease). (2) Patients with conditions such as gastrointestinal bleeding, heart failure, autoimmune diseases, severe liver or kidney dysfunction, or malignancies.

Based on the mRS score 90 days after reperfusion, patients were categorized into the control group (mRS score = 0-3, n = 132) or the study group (mRS score = 4-6, n = 80) [12]. More details are shown in **Figure 1**.

Indicator measurement

At reperfusion, 2-3 mL of peripheral venous blood was collected from each patient, centrifuged at 3000 rpm for 10 minutes, and the serum was stored at 4°C. Levels of CTGF, IL-6, and TNF-α in the serum were measured using enzyme-linked immunosorbent assay kits (IL-6: Shanghai Jining Industrial Co., Ltd., N110863; TNF-α: Shanghai Jingkang Biotechnology Co., Ltd., JKSJ-1857; CTGF: Wuhan Jilide Biotechnology Co., Ltd., J20206).

Outcome measures

Primary outcome measures: (1) Comparison of IL-6, TNF-α, and CTGF levels at reperfusion between the two groups. (2) Analysis of correlations between CTGF, IL-6, and TNF-α levels at reperfusion and mRS and NIHSS scores 90 days post-reperfusion. (3) Identification of factors influencing prognosis through logistic regression analysis.

Secondary outcome measures: (1) Comparison of baseline clinical data between the two groups. (2) Analysis of mRS scores, which range from 0 to 6, with higher scores indicating a worse prognosis [14]. (3) Analysis of NIHSS scores, for assessing stroke severity, with scores ranging from 0 to 42, where higher scores indicate more severe impairment [15].

Statistical analysis

Data analysis was performed using SPSS 20.0. Categorical data were expressed as counts and compared using the χ^2 test, while continuous data with normal distribution were presented as mean ± standard deviation (SD) and compared using the independent samples t-test. The predictive abilities of CTGF, IL-6, and TNF-α were evaluated using Receiver Operating Characteristic (ROC) curve analysis. Logistic regression was conducted to determine factors affecting AIS prognosis. Graphs were generat-

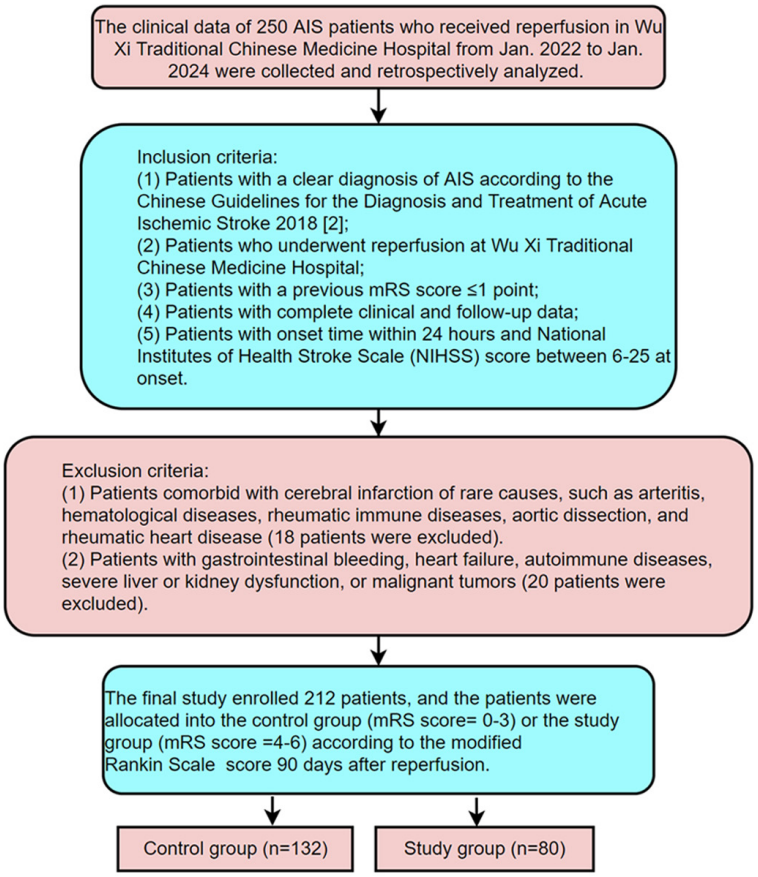

Figure 1. Screening and grouping process.

ed using GraphPad Prism 8. A *P*-value of < 0.05 was considered statistically significant.

Results

Comparison of clinical baseline data

No significant differences were observed between the two groups regarding baseline characteristics, including gender, body mass index (BMI), history of stroke, alcohol consumption, smoking habits, and location of stroke onset (all P > 0.050). However, there were significant differences in age, comorbidities, and previous stroke history (all P < 0.050, **Table 1**).

Comparison of mRS and NIHSS scores 90 days post-reperfusion

Ninety days after reperfusion, the control group had an average mRS score of 1.88 ± 0.77 and a NIHSS score of 7.81 ± 1.93. In contrast, the study group had significantly higher mRS and NIHSS scores, averaging 3.78 ± 0.70 and 16.97 ± 1.55, respectively (both P < 0.001, **Table 2**).

Comparison of IL-6, TNF-α, and CTGF levels at reperfusion

At the time of reperfusion, IL-6, TNF-α, and CTGF levels in the study group were 15.62 ± 6.00 pg/mL, 30.29 ± 6.10 pg/mL, and 872.64 ± 156.36 pg/mL, respectively. In the control group, these levels were significantly lower: 11.36 ± 4.58 pg/mL for IL-6, 26.71 ± 9.21 pg/mL for TNF-α, and 629.56 ± 155.85 pg/mL for CTGF (all P < 0.050, **Figure 2**).

Correlation between IL-6, TNF-α, CTGF levels, and NIHSS scores 90 days post-reperfusion

Statistical analysis showed positive correlations between the levels of IL-6, TNF-α, and CTGF at reperfusion and NIHSS scores 90 days later (IL-6: P < 0.001, r = 0.339; TNF-α: P = 0.006, r = 0.189; CTGF: P < 0.001, r = 0.553, **Figure 3**).

Correlation between IL-6, TNF-α, CTGF levels, and mRS scores 90 days post-reperfusion

Similarly, there were positive correlations between IL-6, TNF-α, and CTGF levels at reperfusion and mRS scores 90 days later (IL-6: P < 0.001, r = 0.324; TNF-α: P = 0.011, r = 0.174; CTGF: P < 0.001, r = 0.461, **Figure 4**).

Predictive value of CTGF, IL-6, TNF-α and their combination on prognosis

The predictive value of CTGF, IL-6, TNF-α, and their combined use for assessing prognosis was evaluated. Receiver Operating Characteristic (ROC) curve analysis demonstrated that the combined prediction using these three biomarkers yielded an area under the curve (AUC) of 0.909, which was higher than the AUC values

Table 1. Comparison of clinical baseline data

	Control group (n = 132)	Study group (n = 80)	χ^2/t	P
Age	68.24 ± 13.49	74.07 ± 8.78	4.523	< 0.0001
Gender			0.135	0.714
Male	76	44		
Female	56	36		
BMI			0.089	0.766
≥ 23 kg/m^2	55	35		
< 23 kg/m^2	77	45		
Comorbid diabetics			4.781	0.029
Yes	20	22		
No	112	58		
Comorbid hypertension			4.372	0.037
Yes	18	20		
No	114	60		
History of stroke			4.189	0.041
Yes	25	25		
No	107	55		
Drinking history			0.338	0.561
Yes	30	21		
No	102	59		
Smoking history			0.301	0.583
Yes	35	24		
No	97	56		
Place of residence			2.066	0.151
Rural area	95	50		
Urban area	37	30		

Note: BMI: body mass index.

Table 2. Comparison of mRS and NHISS scores between the two groups

	mRS 90 days after reperfusion	NHISS 90 days after reperfusion
Control group (n = 132)	1.88 ± 0.77	7.81 ± 1.93
Study group (n = 80)	3.78 ± 0.70	16.97 ± 1.55
t	17.98	35.97
P value	< 0.0001	< 0.0001

Notes: mRS: modified Rankin Scale; NHISS: National Institutes of Health Stroke Scale.

obtained for each individual marker (**Figure 5**; **Table 3**).

Univariate analysis of prognostic factors in patients undergoing reperfusion for AIS

Univariate analysis identified significant differences between the two groups in age, comorbid diabetes, comorbid hypertension, history of stroke, and levels of IL-6, TNF-α, and CTGF at reperfusion (all P < 0.050). These factors were found to influence the prognosis of AIS patients after reperfusion (**Table 4**).

Multivariate logistics regression analysis

A logistic regression analysis was performed using the mRS score as the dependent variable, coded as 1 for scores above 3 and 0 for scores of 3 or below. Covariates included age, comorbid diabetes, comorbid hypertension, history of stroke, and levels of IL-6, TNF-α, and CTGF at reperfusion. In **Table 2**, "comorbid diabetes", "comorbid hypertension", and "history of stroke" were coded as 1 for "Yes" and 0 for "No". The analysis identified age, IL-6, TNF-α, and CTGF levels at reperfusion as independent factors affecting the prognosis of AIS patients post-reperfusion (**Table 5**).

Discussion

Stroke is associated with high rates of incidence, disability, mortality, recurrence, and complications [16]. Among cerebrovascular diseases, AIS is the most common type, usually resulting from blockages in the cerebral arteries that lead to inadequate blood flow and subsequent brain tissue ischemia and hypoxia [17, 18]. Ischemic stroke can severely impair neurological function, causing paralysis, speech difficulties, cognitive deficits, and even death [19]. Reperfusion therapy is critical for AIS treatment, as it rapidly restores blood flow to the ischemic area, reduces brain tissue damage, and improves neurological recovery [20]. Understanding the rela-

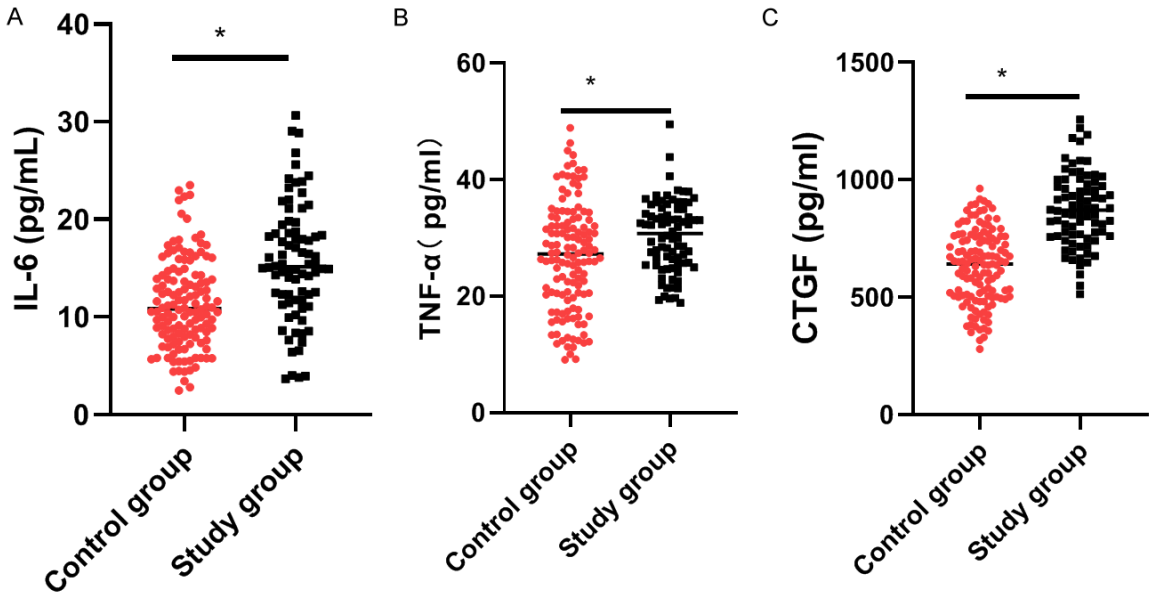

Figure 2. Comparison of IL-6, TNF-α, and CTGF levels at perfusion between the two groups. A: Comparison of IL-6 levels at perfusion between the two groups. B: Comparison of TNF-α levels at perfusion between the two groups. C: Comparison of CTGF levels at perfusion between the two groups. Note: * indicates $P < 0.05$ vs. the control group; CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

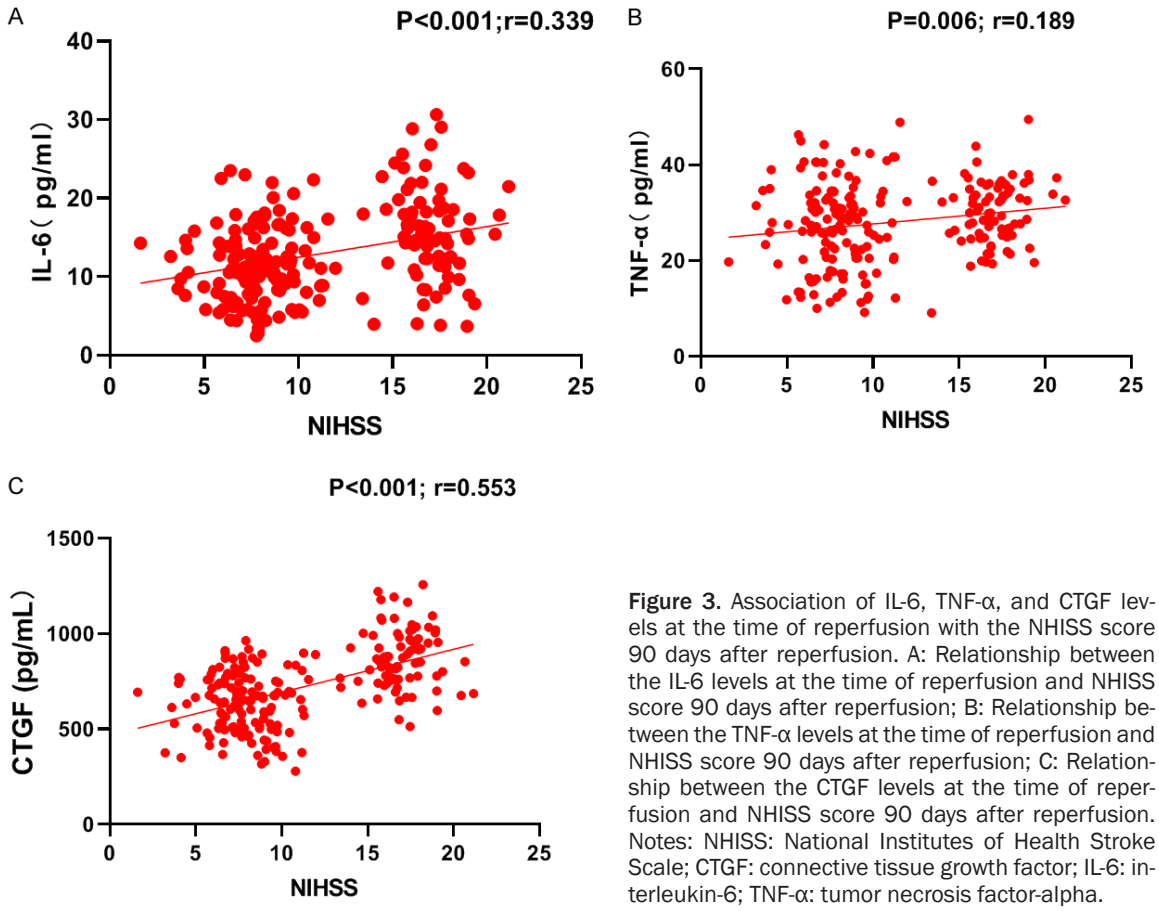

Figure 3. Association of IL-6, TNF-α, and CTGF levels at the time of reperfusion with the NHISS score 90 days after reperfusion. A: Relationship between the IL-6 levels at the time of reperfusion and NHISS score 90 days after reperfusion; B: Relationship between the TNF-α levels at the time of reperfusion and NHISS score 90 days after reperfusion; C: Relationship between the CTGF levels at the time of reperfusion and NHISS score 90 days after reperfusion. Notes: NHISS: National Institutes of Health Stroke Scale; CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

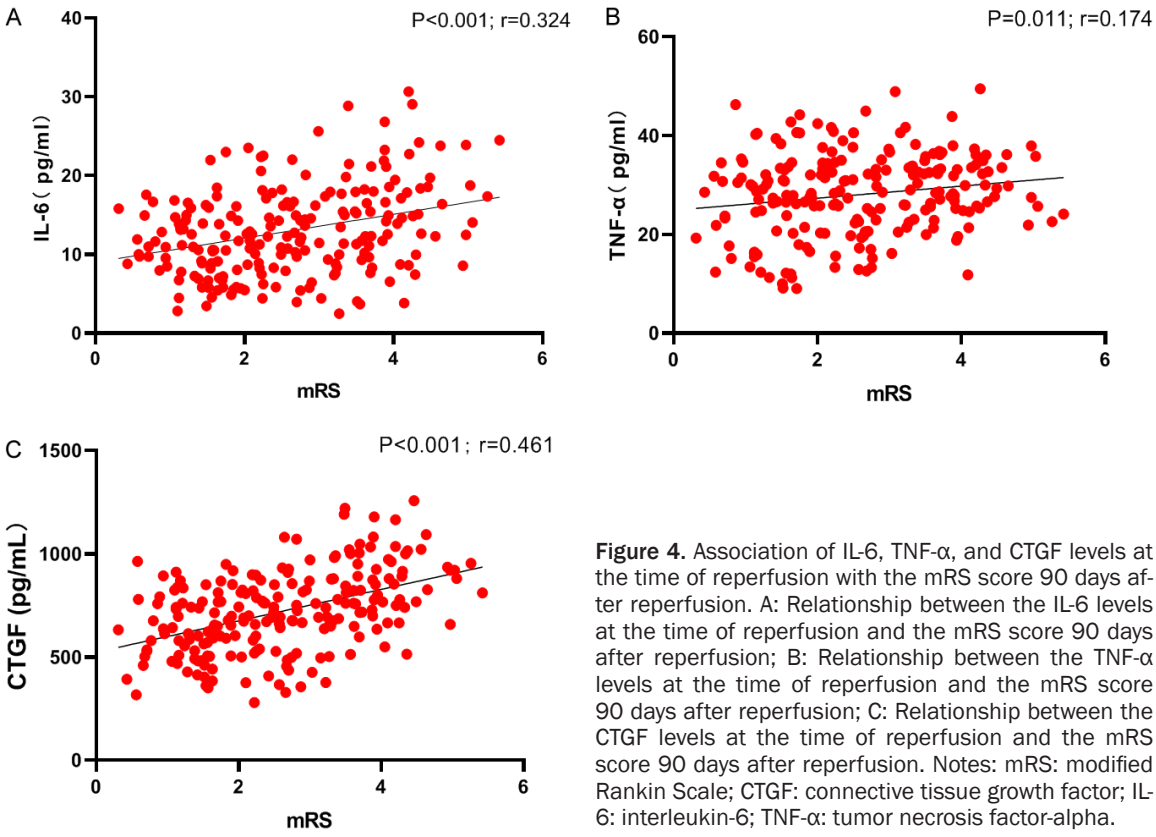

Figure 4. Association of IL-6, TNF-α, and CTGF levels at the time of reperfusion with the mRS score 90 days after reperfusion. A: Relationship between the IL-6 levels at the time of reperfusion and the mRS score 90 days after reperfusion; B: Relationship between the TNF-α levels at the time of reperfusion and the mRS score 90 days after reperfusion; C: Relationship between the CTGF levels at the time of reperfusion and the mRS score 90 days after reperfusion. Notes: mRS: modified Rankin Scale; CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

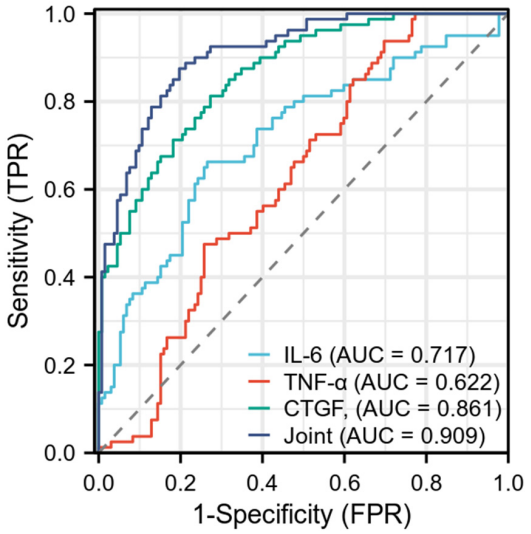

Figure 5. ROC curves of CTGF, IL-6, TNF-α and their combination in predicting the prognosis of patients undergoing reperfusion for AIS. Notes: ROC: Receiver Operating Characteristic; CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; AIS: acute ischemic stroke.

Table 3. Parameters about ROC curves of CTGF, IL-6, TNF-α and their combination in predicting the prognosis of patients undergoing reperfusion for AIS

	AUC	Sensitivity	Specificity	Accuracy
IL-6	0.717	66.25%	73.49%	70.76%
TNF-α	0.622	93.75%	30.30%	54.25%
CTGF	0.861	81.25%	72.73%	75.94%
Joint	0.909	87.50%	80.30%	83.02%

Notes: ROC: receiver operating characteristic; CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; AIS: acute ischemic stroke.

tionship between biomarkers and patient outcomes is crucial for optimizing treatment strategies and enhancing the prognosis of AIS patients undergoing reperfusion. Therefore, this study retrospectively analyzed the levels of CTGF, IL-6, and TNF-α in AIS patients who underwent reperfusion, and assessed their impact on patient prognosis.

The study first analyzed the mRS and NIHSS scores of the patients. The mRS is widely used in clinical practice to evaluate functional status and disability after stroke or other neurological conditions, reflecting a patient's ability to per-

Table 4. Univariate analysis

	Control group (n = 132)	Study group (n = 80)	χ^2/t	P
Age	68.24 ± 13.49	74.07 ± 8.78	4.523	< 0.001
Comorbid diabetics			4.781	0.029
Yes	20	22		
No	112	58		
Comorbid hypertension			4.372	0.037
Yes	18	20		
No	114	60		
History of stroke			4.189	0.041
Yes	25	25		
No	107	55		
IL-6 at the time of reperfusion (pg/ml)	11.36 ± 4.58	15.62 ± 6.00	5.830	< 0.001
TNF-α at the time of perfusion (pg/ml)	26.71 ± 9.21	30.29 ± 6.10	3.089	0.002
CTGF at the time of reperfusion (pg/ml)	629.56 ± 155.85	872.64 ± 156.36	10.99	< 0.001

Notes: CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; AIS: acute ischemic stroke.

Table 5. Multivariate logistics regression analysis

	B	S.E,	Wals	df	Sig.	Exp (B)	95% C.I for EXP (B)	
							Lower limit	Upper limit
Age	0.050	0.019	6.610	1	0.010	1.051	1.012	1.092
IL-6 at the time of reperfusion	0.149	0.041	13.489	1	< 0.001	1.161	1.072	1.257
TNF-α at the time of reperfusion	0.059	0.027	4.568	1	0.033	1.060	1.005	1.119
CTGF at the time of reperfusion	0.011	0.002	41.018	1	< 0.001	1.011	1.008	1.014

Notes: CTGF: connective tissue growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; AIS: acute ischemic stroke.

form daily activities [21, 22]. In contrast, the NIHSS assesses the severity of neurological deficits in stroke patients, with lower scores indicating milder impairment [23, 24]. In this study, patients were grouped based on their mRS scores. The results showed that 90 days post-reperfusion, the control group (mRS score 0-3) had significantly lower NIHSS scores than the study group (mRS score 4-6). This finding highlights the strong association between mRS scores and NIHSS scores, suggesting that as patients recover functionally (indicated by mRS), their neurological deficits (measured by NIHSS) also improve [25].

This study also analyzed IL-6, TNF-α, and CTGF levels at reperfusion, finding that the control group had significantly lower levels of these markers compared to the study group. The association between inflammatory markers and functional recovery highlights the importance of managing inflammation during the acute phase of stroke treatment. Strategies aimed at reducing inflammation and mitigating reperfusion injury could potentially improve patient outcomes and enhance recovery after ischemic stroke [26]. The present study further demonstrated a positive correlation between IL-6, TNF-α, and CTGF levels at reperfusion and the mRS and NIHSS scores 90 days later, suggesting a link between heightened inflammatory responses, tissue damage, and poorer neurological outcomes. Elevated levels of IL-6 and TNF-α indicate increased inflammation, potentially leading to neuronal damage and worse scores on mRS and NIHSS. Meanwhile, higher CTGF levels reflect more severe tissue damage and fibrosis, correlating with poorer prognosis [27]. The elevated levels of these biomarkers at reperfusion likely predict more significant neurological damage within 90 days post-reperfusion, as indicated by both mRS and NIHSS scores [28].

The study also explored the predictive efficacy of combining CTGF, IL-6, and TNF-α for assessing prognosis in AIS patients undergoing reperfusion, providing valuable insights. ROC curve

analysis showed that the combined prediction using these three biomarkers achieved an AUC of 0.909, surpassing the predictive accuracy of each marker individually. This finding suggests that a combined biomarker model may serve as a more robust prognostic tool for AIS patients following reperfusion therapy. The synergistic and complementary information offered by multiple biomarkers likely provides a more comprehensive understanding of inflammatory responses and tissue damage during AIS recovery. Utilizing the combined predictive power of these markers enables clinicians to make more informed decisions, potentially improving outcomes and management of AIS patients post-reperfusion.

Additionally, age, along with IL-6, TNF-α, and CTGF levels at reperfusion, were identified as independent factors influencing AIS prognosis. Older patients may experience slower recovery and face higher risks of comorbidities, affecting their outcomes after reperfusion. Regarding IL-6, TNF-α, and CTGF levels, high levels of these markers can lead to vascular endothelial injury, expansion of the inflammatory response, and neuronal damage, resulting in worse outcomes [29]. Diabetes is also known to be associated with increased risks and poorer prognosis during reperfusion due to vascular injury, inflammation, and metabolic disorders, further exacerbating brain tissue and reperfusion injuries [30, 31]. Lau et al. [30] have found association of diabetes with poor patient outcomes. In contrast, this study did not find diabetes to be a significant factor affecting patient outcomes. This discrepancy could be attributed to the limited sample size of the study. Understanding and evaluating these independent factors can aid clinicians in making more accurate prognostic assessments and developing individualized preventive strategies for AIS patients.

The study has some limitations. First, as a retrospective study, it may be subject to bias from unrecorded or unknown factors despite the advantages in accessing historical data. Second, the limited number of patients may affect the reliability of the conclusions. Future research should involve prospective studies, larger sample sizes, and include more potential influencing factors to improve the robustness of the findings.

In conclusion, in AIS patients undergoing reperfusion, higher levels of CTGF, IL-6, and TNF-α at reperfusion were positively correlated with worse mRS and NIHSS scores 90 days post-reperfusion. Understanding these relationships provides insights into optimizing therapeutic strategies to potentially improve outcomes and recovery in ischemic stroke reperfusion therapy. Additionally, age and levels of IL-6, TNF-α, and CTGF at reperfusion were identified as independent factors affecting prognosis.

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Disclosure of conflict of interest

None.

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