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Original Article

Efficacy, safety, and effect on platelet activation of the timing of administration of tirofiban in patients with acute ischemic stroke

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Abstract: Objective: To evaluate the efficacy, safety, and effects on platelet activation of tirofiban administered at different times in patients with acute ischemic stroke, with the goal of providing precise guidance for clinical treatment timing. Methods: A total of 262 patients with acute ischemic stroke admitted to No. 215 Hospital of Shaanxi Nuclear Industry between January 2021 and June 2023 were retrospectively analyzed. Patients were divided into an early treatment group (ETG, n = 124) and a late treatment group (LTG, n = 138) based on the timing of tirofiban administration. The ETG received tirofiban within 6 hours after thrombolysis, while the LTG received it 6 to 24 hours after thrombolysis. Clinical efficacy was evaluated post-treatment, and adverse reactions during treatment were recorded. Comparisons were made for pre- and post-treatment National Institutes of Health Stroke Scale (NIHSS) scores, Modified Rankin Scale (mRS) scores, neurological function markers, coagulation factors, inflammatory markers, and homocysteine (Hcy) levels. Correlations between efficacy and post-treatment indicators were analyzed, and logistic regression identified factors influencing outcome. Results: The ETG demonstrated significantly better overall efficacy than the LTG (P = 0.004). Post-treatment NIHSS and mRS scores, neuron-specific enolase (NSE), platelet-activating factor (PAF), high-sensitivity C-reactive protein (hs-CRP), Hcy, and interleukin-1β (IL-1β) levels were significantly lower in the ETG, while brain-derived neurotrophic factor (BDNF) levels were higher (all P < 0.001). Clinical efficacy correlated significantly with post-treatment mRS scores, PAF levels, and Hcy levels (all P < 0.001). The ETG also had significantly lower rates of re-occlusion (P = 0.001), cardiopulmonary complications (P = 0.004), and symptomatic cerebral hemorrhage (P = 0.035). Logistic regression showed that the LTG was associated with reduced efficacy (β = -4.469, P = 0.019), while higher post-treatment PAF (β = 2.437, P < 0.001) and Hcy levels (β = 1.782, P = 0.013) were linked to poorer outcome. Conclusion: Early administration of tirofiban in acute ischemic stroke offers significant clinical benefits, including improved neurological function and enhanced daily living abilities, with reduced inflammatory response and complications.

Keywords: Acute ischemic stroke, tirofiban, efficacy, safety, neurological function

Introduction

Stroke, or cerebrovascular accident, is a major acute cerebrovascular disease characterized by high rates of incidence, disability, mortality, and recurrence [1]. It is classified into hemorrhagic and ischemic stroke, with ischemic stroke being more common, accounting for 60-70% of cases [2]. Typically caused by lesions in the internal carotid and vertebral arteries, severe ischemic stroke can lead to death. Stroke is a leading cause of death in China and ranks as the second leading cause of death and third leading cause of disability worldwide [3]. Acute ischemic stroke, triggered by cerebral artery occlusion, results in damage to neurons and astrocytes, making it a significant cause of death and disability [4]. This condition is prevalent among middle-aged and elderly individuals, with a growing trend of earlier onset in younger populations [5]. The increasing incidence and mortality of cardiovascular and cerebrovascular diseases, driven by population growth and aging, have imposed a substantial burden on healthcare in China [6]. Early recognition of stroke symptoms and standardized treatment

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within 4.5 hours of onset are crucial for improving patient outcome and quality of life.

The cornerstone of acute ischemic stroke treatment is the timely reopening of occluded vessels to salvage the ischemic penumbra. Intravenous thrombolysis is the primary strategy for restoring blood flow, with agents like recombinant tissue plasminogen activator (rt-PA), urokinase, and tenecteplase showing greater efficacy with earlier administration [7, 8]. Clinical outcomes improve significantly when alteplase is administered within 4.5 hours of symptom onset, or urokinase within 6 hours [9]. However, most patients present to the hospital beyond this critical window, rendering them ineligible for thrombolysis and increasing the risk of severe complications such as hemiplegia or death [10, 11]. Endovascular interventions, including arterial thrombolysis and mechanical thrombectomy, have increased recanalization rates, yet concerns about their safety and efficacy remain [12].

Anticoagulant and antiplatelet therapies are widely used in the acute phase and for secondary prevention, but their efficacy and safety remain under debate. While antiplatelet agents such as aspirin and clopidogrel are effective, they have a slow onset of action and irreversible effects [13, 14]. Consequently, identifying more effective early interventions is critical to improving outcomes in acute ischemic stroke. Tirofiban, a potent inhibitor of platelet aggregation, has been widely used in cardiovascular disease management [15]. However, its optimal timing for acute ischemic stroke treatment remains unclear. Current clinical practice lacks consensus on whether early or late administration of tirofiban offers better patient outcomes [16, 17]. Addressing this gap in evidence is essential for rationalizing the use of tirofiban in acute ischemic stroke.

This study aims to investigate the efficacy and safety of tirofiban administered at different timings in patients with acute ischemic stroke. By comparing the effects of administration within 6 hours and between 6-24 hours post-thrombolysis on indicators such as neurological function, daily living ability, and inflammatory markers, this research seeks to determine the optimal timing for tirofiban use. The findings should provide new clinical evidence to guide the treatment of acute ischemic stroke, clarify the benefits and risks of tirofiban timing, and inform strategies to improve prognosis while reducing stroke-related disability and mortality.

Materials and methods

Sample size calculation

Based on the study by Bao et al. [18], the overall effectiveness rate was 91.30% in the observation group and 75.56% in the control group. The mean effectiveness was calculated as (91.30% + 75.56%)/2 = 83.43%. Using the formula $N = Z^2 \times [P \times (1\text{-}P)]/E^2$, where Z = 1.96 (95% confidence level), P = 0.8343 (83.43%), and E = 0.05 (5% margin of error), the sample size is calculated as follows: $N = 1.96^2 \times [0.8343 \times (1\text{-}0.8343)]/0.05^2 = 212.36$. Thus, the required sample size is approximately 213 patients. Actual sample collection should consider clinical conditions, including patient availability and inclusion/exclusion criteria.

Patient information

This study retrospectively analyzed 262 patients with acute ischemic stroke admitted to No. 215 Hospital of Shaanxi Nuclear Industry between January 2021 and June 2023. Patients were divided into an early treatment group (ETG, n = 124) and a late treatment group (LTG, n = 138) based on the timing of tirofiban administration. The ETG received tirofiban within 6 hours post-thrombolysis, while the LTG received it between 6 and 24 hours post-thrombolysis.

The timing of treatment was primarily determined by the patient's or their family's decision after being informed by the physician. Physicians made recommendations based on the patient's condition, but variations in decision-making time resulted in differing treatment times. This variability provided the study with treatment samples across different time points.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients meeting the diagnostic criteria for acute ischemic stroke per the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke [19], confirmed by imaging studies. (2) First stroke onset, with time from onset to admission < 4.5 hours. (3) All patients received intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) after admission. (4)

Complete clinical data available, including Brain-Derived Neurotrophic Factor (BDNF), Neuron-Specific Enolase (NSE), and Platelet-Activating Factor (PAF).

Exclusion criteria: (1) History of gastrointestinal bleeding, genitourinary bleeding, hemorrhagic retinopathy, or severe physical trauma. (2) Presence of malignant tumors, coagulation disorders, abnormal platelet counts, or undergoing chronic hemodialysis. (3) Allergy to tirofiban injection or recent use of antiepileptic or dopamine-related drugs within the past three months.

Treatment protocol

All enrolled patients received intravenous thrombolysis with recombinant tissue rt-PA, provided by Boehringer Ingelheim Pharmaceuticals (China) Co., Ltd. (National Drug Approval Number: S20150001). The dosage was 0.9 mg/kg per dose, with 10% administered as a bolus injection over 10 minutes and the remaining 90% delivered via drip infusion over 1 hour, once daily. A follow-up computed tomography (CT) scan was performed 24 hours post-administration.

Additionally, patients received aspirin (Bayer (China) Co., Ltd., National Drug Approval Number: H37020354) at a dose of 100 mg daily for 7 consecutive days. Based on group assignments, the ETG (n = 124) received tirofiban within 6 hours post-thrombolysis, while the LTG (n = 138) received tirofiban 6-24 hours post-thrombolysis. The dosage and frequency of tirofiban administration were identical for both groups: an initial intravenous dose of 0.4 μg/kg/min over 30 minutes, followed by a continuous infusion at 0.075 μg/kg/min for 48 hours.

Functional scoring

Neurological function and daily living ability were assessed using the National Institutes of Health Stroke Scale (NIHSS) [20] and the Modified Rankin Scale (mRS) [21]. The NIHSS evaluates the severity of neurological deficits in acute stroke patients, including factors such as consciousness, eye movement, visual field, facial movement, limb movements, language, articulation, and attention. Scores range from 0 to 42, with higher scores indicating more severe neurological impairment.

The mRS assesses recovery of daily living ability and independence. Recovery classifications include: Basic recovery: 91%-100% improvement. Effective: 30%-90% improvement. Ineffective: Less than 30% improvement or worsening.

The total response rate is calculated as: Total response rate = (basic recovery + effective) cases/total cases 100%. The mRS score ranges from 0 to 6, where 0 indicates no symptoms and 6 indicates death.

Laboratory indicator testing

A range of laboratory indicators were measured during the study: Routine blood Indicators: White blood cell count, red blood cell count, hemoglobin, hematocrit, and platelet count were measured using the Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Japan). Biochemical Indicators: Renal function markers (urea, serum creatinine, uric acid) and myocardial enzyme markers (creatine kinase, lactate dehydrogenase, creatine kinase-MB), as well as Homocysteine (Hcy) and inflammatory markers like high-sensitivity C-reactive protein (hs-CRP), were measured using the AU5800 automated biochemical analyzer (Beckman Coulter, USA). Coagulation Indicators: Prothrombin time, International Normalized Ratio (INR), fibrinogen, thrombin time, and activated partial thromboplastin time were assessed using the CS-1300 automated coagulation analyzer (Sysmex Corporation, Japan). Neurological Indicators: BDNF and NSE levels were analyzed using the AU5800 biochemical analyzer (Beckman Coulter). Platelet Activation and Inflammation Markers: Platelet-Activating Factor (PAF) and Interleukin-1β (IL-1β) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits provided by Shanghai Enzyme-linked Biotechnology Co., Ltd.

Clinical data collection

Patient clinical information, including laboratory indicators and functional scores, was collected through the Laboratory Information System (LIS). Specific laboratory indicators included white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, urea, serum creatinine, uric acid, Hcy, creatine kinase, lactate dehydrogenase, cre-

Table 1. Comparison of baseline characteristics of patients

Factor	Total	Late Treatment Group (n = 124)	Early Treatment Group (n = 138)	Statistic Value	*P*-value
Age					
≥ 60 years	149	69	80	0.144	0.704
< 60 years	113	55	58		
Sex					
Male	171	84	87	0.636	0.425
Female	91	40	51		
BMI					
≥ 25 kg/m^2	55	29	26	0.814	0.367
< 25 kg/m^2	207	95	112		
History of Hypertension				0.242	0.622
Yes	198	92	106		
No	64	32	32		
History of Diabetes				0.807	0.369
Yes	68	29	39		
No	194	95	99		
History of Stroke					
Yes	52	22	30	0.656	0.418
No	210	102	108		
History of Coronary Artery Disease				0.162	0.688
Yes	12	5	7		
No	250	119	131		
Smoking History					
Yes	75	41	34	2.270	0.132
No	187	83	104		
Drinking History					
Yes	40	22	18	1.115	0.291
No	222	102	120		
White Blood Cells (×10^9/L)	7.00±1.55	6.97±1.46	7.04±1.62	-0.356	0.722
Red Blood Cells (×10^{12}/L)	4.80 (4.50-5.00)	4.80 (4.47-5.00)	4.75±0.31	-0.229	0.818
Hemoglobin (g/L)	135.53±15.02	137.04±14.09	134.17±15.75	1.559	0.120
Hematocrit (%)	41.19±5.00	40.90±5.61	41.45±4.39	-0.882	0.379
Platelets (×10^9/L)	236.68±38.33	240.26±37.68	233.47±38.76	1.436	0.152
Urea (mmol/L)	4.95±1.00	4.89±0.87	5.01±1.11	-0.998	0.319
Serum Creatinine (μmol/L)	80.79±11.95	80.91±12.02	80.68±11.92	0.159	0.874
Uric Acid (μmol/L)	339.84±100.79	340.29±78.11	339.42±117.79	0.071	0.944
Creatine Kinase (U/L)	93.09±30.57	88.34±29.99	97.36±30.56	-2.41	0.017
Lactate Dehydrogenase (U/L)	190.47±26.56	190.54±29.33	190.41±23.90	0.040	0.968
Creatine Kinase-MB (U/L)	18.00 (16.00-21.00)	17.67±3.63	19.00 (16.00-21.00)	-1.939	0.052
Prothrombin Time (seconds)	11.00 (10.70-11.40)	11.10 (10.70-11.40)	10.99±0.52	0.660	0.509
International Normalized Ratio (INR)	0.94±0.08	0.94±0.08	0.94±0.08	0.796	0.427
Fibrinogen (g/L)	3.02±0.51	2.99±0.53	3.04±0.48	-0.837	0.403
Thrombin Time (seconds)	16.47±1.95	16.46±2.14	16.47±1.77	-0.04	0.968
Activated Partial Thromboplastin Time (seconds)	25.20±1.70	25.34±1.63	25.07±1.76	1.302	0.194

Note: BMI, Body Mass Index.

atine kinase-MB, hs-CRP, BDNF, NSE, PAF, and IL-1β. Functional scores, including the NIHSS and mRS, were collected alongside data on adverse reactions during treatment and efficacy assessments.

Outcome measures

Primary outcome measures: Clinical efficacy after treatment and the incidence of adverse reactions during treatment.

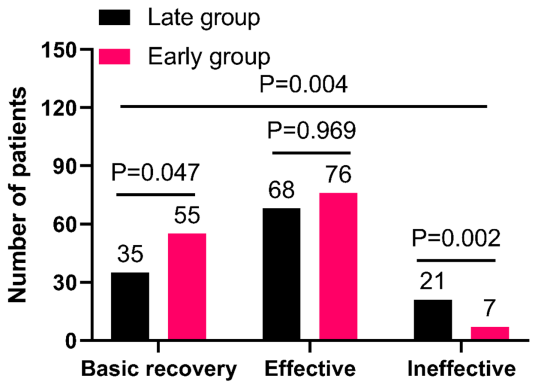


Figure 1. Comparison of the number of patients with basic recovery, effective treatment, and ineffective treatment between the two groups after treatment.

Secondary outcome measures: Changes in NIHSS and mRS scores, neurological function indicators, coagulation factors, inflammatory factors, and Hcy levels before and after treatment; correlation analysis between treatment efficacy and post-treatment indicators. Logistic regression was conducted to identify risk factors influencing post-treatment efficacy.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Normality tests were conducted for continuous variables to determine distribution patterns.

For normally distributed variables, between-group comparisons were done using the Independent Samples t-test, and within-group comparisons were performed using the Paired Samples t-test. For non-normally distributed variables between-group comparisons were conducted using the Mann-Whitney U test, and within-group comparisons were performed using the Wilcoxon signed-rank test.

Categorical variables were compared using the chi-square test to evaluate baseline characteristics and adverse event rates.

Multivariate logistic regression analysis was performed to assess the independent effects of various factors on treatment outcomes and identify risk factors associated with efficacy. Given that treatment efficacy was treated as an ordinal variable, Spearman's rank correlation coefficient was used to explore relationships between efficacy and functional or laboratory indicators.

Data visualization was conducted using R (primarily the ggplot2 package) to graphically represent results and elucidate relationships between variables. All statistical tests were two-sided, with *P*-values < 0.05 considered significant.

Results

Comparison of baseline characteristics

Statistical analysis of baseline characteristics revealed no significant differences between the groups (**Table 1**, all P > 0.05).

Comparison of clinical efficacy

The evaluation of clinical efficacy demonstrated significant differences between the two groups in terms of basic recovery rate and the number of patients with ineffective treatment. The ETG exhibited a higher basic recovery rate (P = 0.047) and fewer patients with ineffective treatment (P = 0.002). However, no significant difference was observed in the rate of significant improvement between the groups (P = 0.969). Overall, the clinical efficacy in the ETG was significantly better than that in the LTG (P = 0.004) (**Figure 1**).

Comparison of neurological function and daily living ability

Before treatment, there were no significant differences in NIHSS or mRS scores between the groups (both P > 0.05). After treatment, the ETG demonstrated significant improvements in both NIHSS and mRS scores compared to the LTG (both P < 0.001) (**Figure 2**).

Comparison of neurological function indicators and coagulation factor levels

Before treatment, BDNF, NSE, and PAF levels were similar between the two groups (all P > 0.05). After treatment, BDNF levels in the ETG were significantly higher than in the LTG (P < 0.001), while NSE and PAF levels were significantly lower (both P < 0.001) (**Figure 3**).

Comparison of inflammatory factors and Hcy levels

Before treatment, hs-CRP, Hcy, and IL-1β levels were comparable between the groups (all P > 0.05). Following treatment, the ETG exhibited significantly reduced levels of hs-CRP, Hcy, and

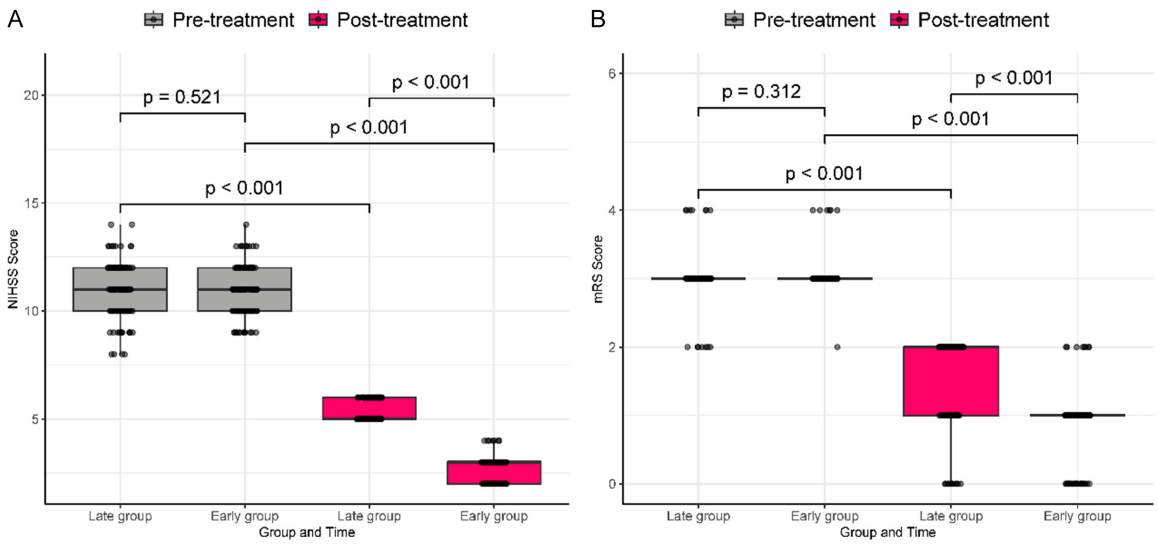


Figure 2. Comparison of NIHSS and mRS scores between different groups before and after treatment. A: Comparison of NIHSS scores between the two groups before treatment (gray) and after treatment (pink). There was no significant difference between the two groups before treatment (P = 0.521), but after treatment, the NIHSS scores in the early treatment group were significantly lower than in the late treatment group (P < 0.001). B: Comparison of mRS scores between the two groups before treatment (gray) and after treatment (pink). There was no significant difference between the two groups before treatment (P = 0.312), but after treatment, the mRS scores in the early treatment group were significantly lower than in the late treatment group (P < 0.001). Note: NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale.

IL-1β compared to the LTG (all P < 0.001) (**Figure 4**).

Significant correlations between efficacy and post-treatment indicators

Correlation analysis revealed significant associations between clinical efficacy and post-treatment mRS scores, PAF levels, and Hcy levels (all P < 0.001), with the strongest correlation observed for PAF levels (r = 0.724). Conversely, no significant correlations were found between clinical efficacy and post-treatment NIHSS scores, BDNF, NSE, hs-CRP, or IL-1β levels (both P > 0.05) (**Table 2**; **Figure 5**).

Comparison of incidence of adverse reactions

Analysis demonstrated that the overall incidence of symptomatic cerebral hemorrhage, re-occlusion, and cardiopulmonary complications was significantly lower in the ETG compared to the LTG (P < 0.001). Specifically, the ETG had a significantly lower incidence of re-occlusion (P = 0.001) and cardiopulmonary complications (P = 0.004), along with a reduced incidence of symptomatic cerebral hemorrhage (P = 0.035). These results highlight that early treatment not only mitigates the risk of re-occlusion but also reduces cardiopulmonary complications, thereby improving overall patient prognosis (**Figure 6**).

Risk factors affecting treatment efficacy

Univariate analysis revealed significant differences in treatment grouping (P = 0.002), post-treatment NIHSS score (P = 0.005), post-treatment mRS score (P < 0.001), post-treatment PAF level (P < 0.001), post-treatment hs-CRP level (P = 0.002), post-treatment Hcy level (P < 0.001), and post-treatment IL-1β level (P = 0.002) between the improvement and ineffective groups. Other variables, such as age, sex, and BMI, did not show significant differences (**Table 3**).

Multivariate logistic regression analysis confirmed these findings. Patients in the late treatment group had significantly lower efficacy compared to those in the early treatment group (β = -4.469, P = 0.019). Additionally, post-treatment PAF level (β = 2.437, P < 0.001) and post-treatment Hcy level (β = 1.782, P = 0.013) were significantly associated with efficacy. However, post-treatment NIHSS score, mRS score, hs-

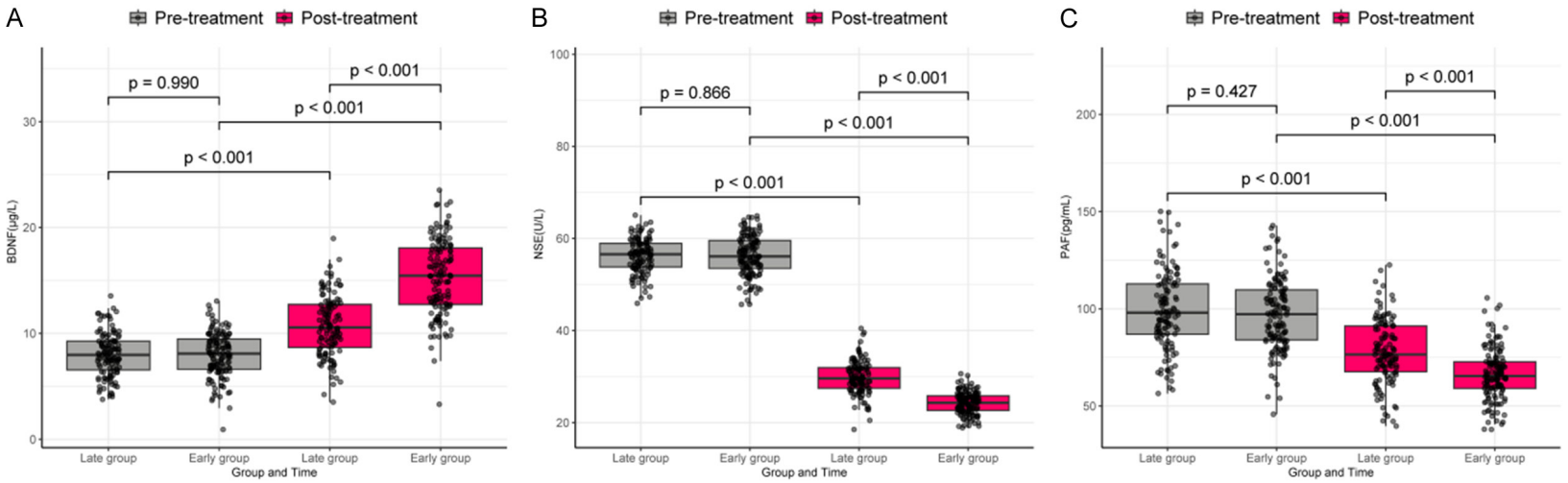


Figure 3. Comparison of BDNF, NSE, and PAF levels between different groups before and after treatment. A: Comparison of BDNF levels between the two groups before treatment (gray) and after treatment (pink). There was no significant difference between the two groups before treatment (P = 0.990), but after treatment, the BDNF levels in the early treatment group were significantly higher than in the late treatment group (P < 0.001). B: Comparison of NSE levels between the two groups before and after treatment. There was no significant difference between the two groups before treatment (P = 0.866), but after treatment, the NSE levels in the early treatment group were significantly lower than in the late treatment group (P < 0.001). C: Comparison of PAF levels between the late treatment group and the early treatment group before and after treatment. There was no significant difference between the two groups before treatment (P = 0.427), but after treatment, the PAF levels in the early treatment group were significantly lower than in the late treatment group (P < 0.001). Note: BDNF, Brain-Derived Neurotrophic Factor; NSE, Neuron-Specific Enolase; PAF, Platelet-Activating Factor.

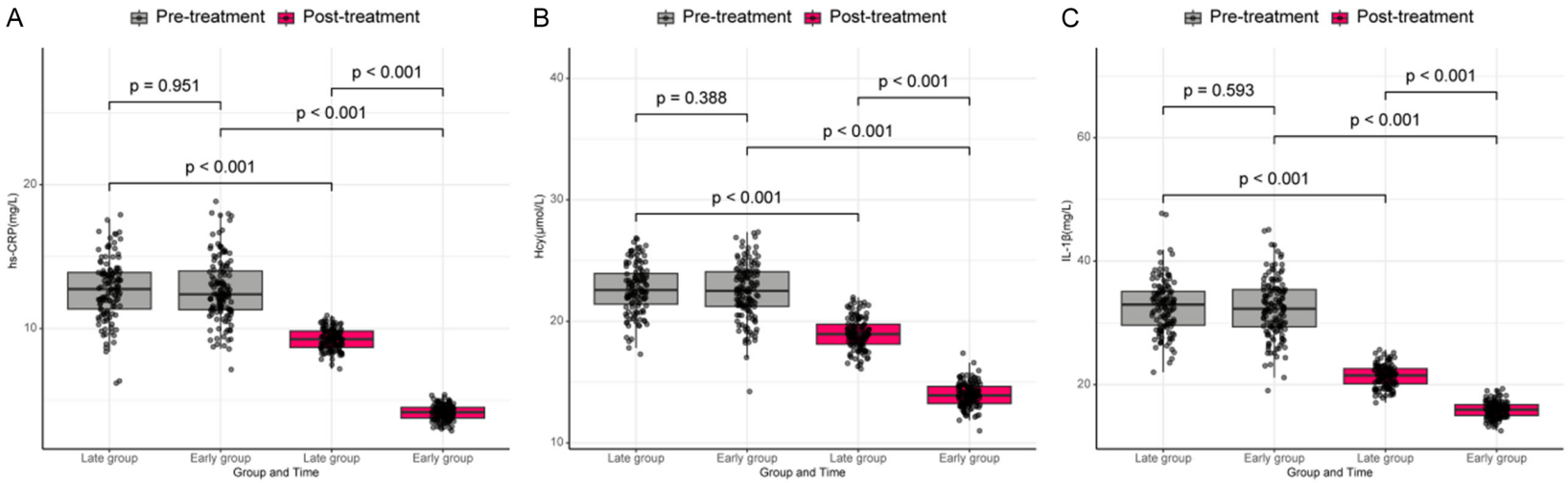


Figure 4. Comparison of hs-CRP, Hcy, and IL-1β levels between different groups before and after treatment. A: Comparison of hs-CRP levels between the late treatment group and the early treatment group before (gray) and after treatment (pink). There was no significant difference between the two groups before treatment (P = 0.951), but after treatment, the hs-CRP levels in the early treatment group were significantly lower than in the late treatment group (P < 0.001). B: Comparison of Hcy levels between the two groups before and after treatment. There was no significant difference between the two groups before treatment (P = 0.388), but after treatment, the Hcy levels in the early treatment group were significantly lower than in the late treatment group (P < 0.001). C: Comparison of IL-1β levels between the two groups before and after treatment. There was no significant difference between the two groups before treatment (P = 0.593), but after treatment, the IL-1β levels in the early treatment group were significantly lower than in the late treatment group (P < 0.001). Note: hs-CRP, High-sensitivity C-reactive Protein; Hcy, Homocysteine; IL-1β, Interleukin-1β.

Table 2. Correlation analysis between efficacy and post-treatment indicators

Variable	Variable	R value	*P* value
Clinical Efficacy	Post-treatment NIHSS score	0.084	0.176
	Post-treatment mRS score	0.536	< 0.001
	Post-treatment BDNF	-0.029	0.644
	Post-treatment NSE	0.063	0.312
	Post-treatment PAF	0.724	< 0.001
	Post-treatment hs-CRP	0.058	0.349
	Post-treatment Hcy	0.368	< 0.001
	Post-treatment IL-1β	0.117	0.058

Note: NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; BDNF, Brain-Derived Neurotrophic Factor; NSE, Neuron-Specific Enolase; PAF, Platelet-Activating Factor; hs-CRP, High-sensitivity C-reactive Protein; Hcy, Homocysteine; IL-1β, Interleukin-1β.

CRP level, and IL-1β level were not significant in the multivariate analysis (all P < 0.05, **Figure 7**).

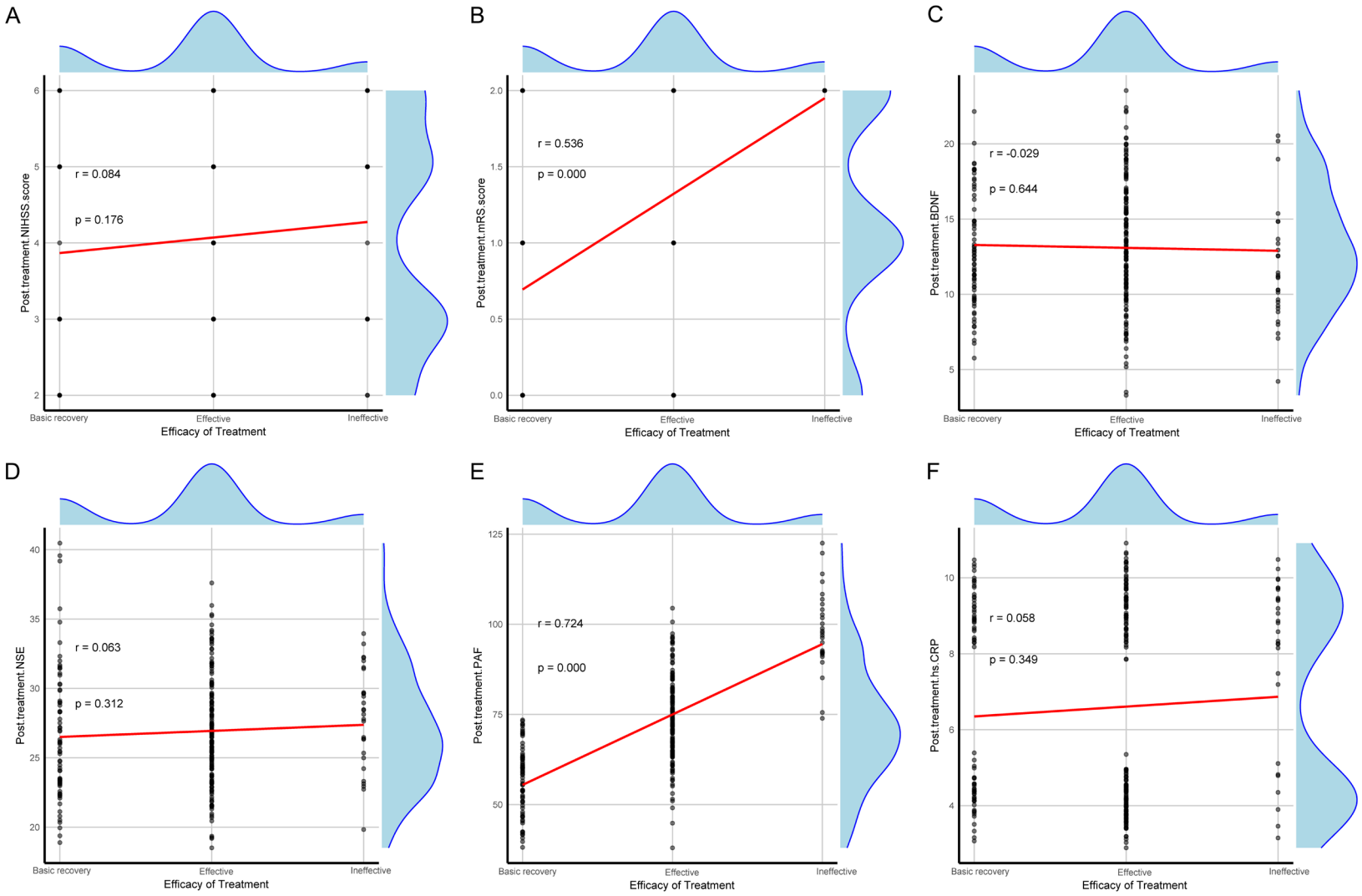
Discussion

This study investigated the clinical efficacy and safety of tirofiban administered at different time windows in patients with acute ischemic stroke. The early treatment group (ETG) demonstrated significant advantages over the late treatment group (LTG) across various clinical indicators. Specifically, the ETG showed greater improvements in neurological function and daily living ability, as reflected by lower NIHSS and mRS scores. Additionally, inflammatory markers such as hs-CRP, Hcy, and IL-1β were significantly reduced in the ETG, highlighting the benefits of early tirofiban administration in controlling the inflammatory response. Furthermore, the incidence of adverse reactions, including re-occlusion and cardiopulmonary complications, was significantly lower in the ETG, underscoring the importance of early treatment in improving patient outcomes.

These findings align with previous studies while also providing new insights. Prior research has shown that tirofiban, a potent platelet aggregation inhibitor, achieves favorable outcomes in cardiovascular disease management [22-24]. However, the optimal timing of tirofiban use in acute ischemic stroke remains debated. Some studies suggest that early administration can significantly enhance prognosis. For instance, Li et al. found that early tirofiban use improved recanalization rates and reduced infarct volume after thrombolysis [25]. Similarly, Jung et al. reported that faster thrombolytic therapy enhanced functional outcomes and reduced complications [26]. A meta-analysis by Kaesmacher et al. also indicated that early combined thrombolysis and mechanical thrombectomy significantly improved functional outcomes [27].

Conversely, concerns about increased bleeding risk with early tirofiban use have been raised. Tang et al., in a meta-analysis, reported no significant increase in symptomatic intracranial hemorrhage associated with tirofiban in acute ischemic stroke [28]. By comparing the two groups, this study demonstrated that early tirofiban administration not only improved neurological and inflammatory markers but also did not significantly increase bleeding-related complications. These results provide new perspectives, reinforcing the clinical value of early tirofiban use.

The mechanism of action of tirofiban in acute ischemic stroke primarily involves inhibiting platelet aggregation and promoting vascular recanalization. Rapid restoration of cerebral blood flow in the early stages of stroke is critical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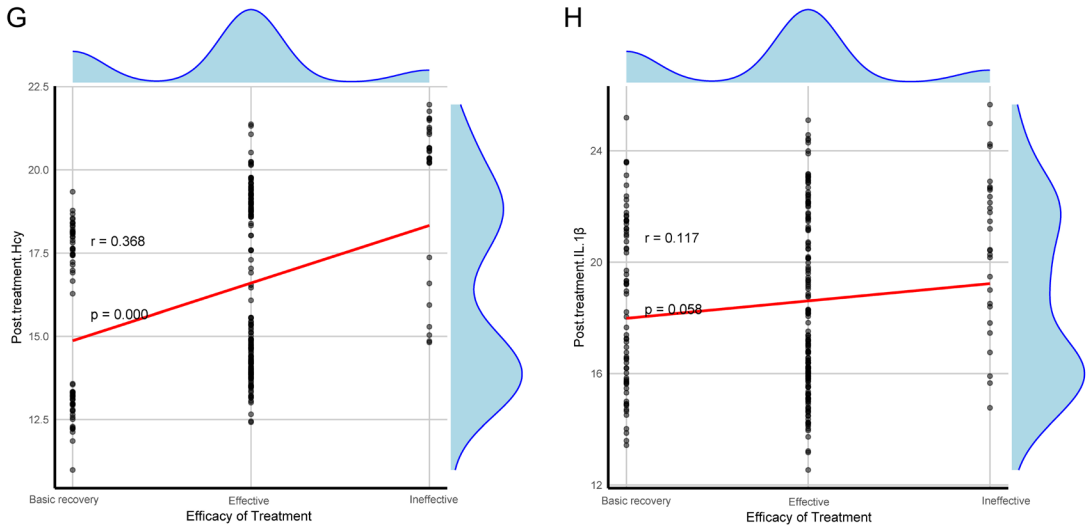

Figure 5. Correlation between clinical efficacy and various post-treatment indicators. A: Correlation between clinical efficacy and post-treatment NIHSS score (r = 0.084, P = 0.176). B: Correlation between clinical efficacy and post-treatment mRS score (r = 0.536, P < 0.001). C: Correlation between clinical efficacy and post-treatment BDNF levels (r = -0.029, P = 0.644). D: Correlation between clinical efficacy and post-treatment NSE levels (r = 0.063, P = 0.312). E: Correlation between clinical efficacy and post-treatment PAF levels (r = 0.724, P < 0.001). F: Correlation between clinical efficacy and post-treatment hs-CRP levels (r = 0.058, P = 0.349). G: Correlation between clinical efficacy and post-treatment Hcy levels (r = 0.368, P < 0.001). H: Correlation between clinical efficacy and post-treatment IL-1β levels (r = 0.117, P = 0.058). Note: NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; BDNF, Brain-Derived Neurotrophic Factor; NSE, Neuron-Specific Enolase; PAF, Platelet-Activating Factor; hs-CRP, High-sensitivity C-reactive Protein; Hcy, Homocysteine; IL-1β, Interleukin-1β.

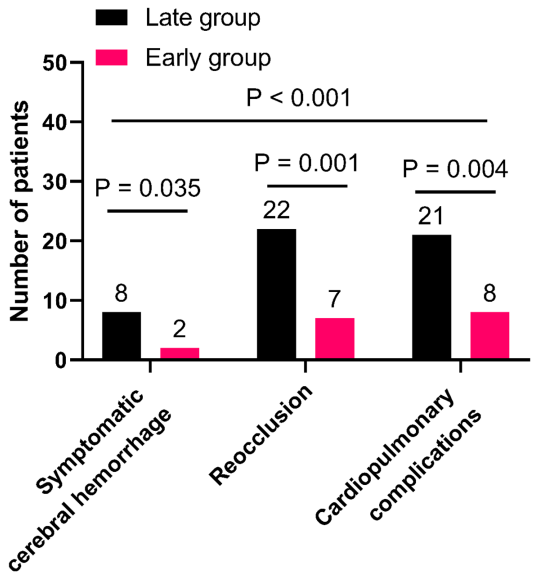

Figure 6. Comparison of complication rates between different groups of patients.

for salvaging the ischemic penumbra and mitigating neuronal damage [29]. Kaesmacher et al. further emphasized the benefits of early combined thrombolysis and thrombectomy in improving functional outcome [27]. Tirofiban inhibits platelet aggregation by targeting IIb/IIIa receptors, reducing thrombosis risk and promoting recanalization. This was evidenced in our study, where the ETG exhibited significant improvements in NIHSS and mRS scores.

Moreover, tirofiban appears to modulate the inflammatory response. Liu et al. highlighted the role of post-stroke inflammation in exacerbating neurological damage [30]. Consistent with this, our study showed that early tirofiban administration significantly reduced hs-CRP, Hcy, and IL-1β levels, suggesting that its anti-inflammatory effects contribute to improved neurological function and prognosis.

The multivariate logistic regression analysis in this study identified post-treatment PAF and Hcy levels as significant risk factors influencing treatment outcome. PAF, an important inflammatory mediator, has been shown to be closely associated with thrombosis and inflammatory responses in various diseases [31]. Studies have demonstrated [32] that elevated PAF levels can exacerbate thrombosis and inflammation by promoting platelet aggregation and leukocyte adhesion, adversely affecting prognosis. In patients with acute ischemic stroke, tirofiban may enhance clinical outcome by inhibiting PAF activity, thereby reducing platelet aggregation and inflammatory responses.

Similarly, Hcy is a well-established biomarker associated with stroke prognosis. Elevated Hcy levels are a recognized risk factor for endothelial dysfunction and thrombosis [33]. Hcy exacerbates brain tissue damage by inducing oxidative stress and inflammatory responses. Tirofiban may improve neurological function and daily living ability by lowering Hcy levels and minimizing endothelial damage [34]. In this study, the early treatment group exhibited significantly lower Hcy levels than the LTG, suggesting that early tirofiban administration effectively reduces Hcy levels, thereby improving prognosis.

The findings of this study have important implications for clinical practice. First, the results support the use of tirofiban as an adjunctive treatment within 6 hours after thrombolysis in acute ischemic stroke to enhance thrombolysis efficacy, improve neurological function, and increase daily living ability. Second, early tirofiban use demonstrated significant efficacy advantages without a notable increase in adverse reactions, providing critical evidence for clinicians when selecting treatment strategies.

As personalized treatment gains prominence, this study offers valuable evidence for optimizing treatment regimens for acute ischemic stroke. Early administration of tirofiban should be prioritized, taking into account the patient's condition severity and the thrombolysis time window.

Despite its valuable findings, this study has several limitations. First, as a retrospective analysis, it may have been subject to selection and information biases. Second, the relatively small sample size and single-center design may limit the generalizability of the results. Third, treatment timing was primarily determined by the patient or their family, possibly resulting in milder cases being assigned to the LTG, which could affect result accuracy. Lastly, the study did not assess long-term patient outcomes. Future research should aim to validate these findings through prospective, randomized controlled trials and explore the long-term

Table 3. Univariate analysis

Factor	Total	Improvement Group (n = 234)	Ineffective Group (n = 28)	Statistic Value	*P*-value
Treatment Group					
Late Treatment Group	124	103	21	9.630	0.002
Early Treatment Group	138	131	7		
Age					
≥ 60 years	149	134	15	0.139	0.709
< 60 years	113	100	13		
Sex					
Male	171	149	22	2.448	0.118
Female	91	85	6		
BMI					
≥ 25 kg/m^2	55	53	2	3.626	0.057
< 25 kg/m^2	207	181	26		
History of Hypertension				1.011	0.315
Yes	198	179	19		
No	64	55	9		
History of Diabetes				0.015	0.903
Yes	68	61	7		
No	194	173	21		
History of Stroke					
Yes	52	48	4	0.610	0.435
No	210	186	24		
History of Coronary Artery Disease				1.505	0.220
Yes	12	12	0		
No	250	222	28		
Smoking History					
Yes	75	65	10	0.771	0.380
No	187	169	18		
Drinking History					
Yes	40	37	3	0.502	0.478
No	222	197	25		
White Blood Cells (×10^9/L)	7.00±1.55	7.03±1.55	6.79±1.53	-0.781	0.440
Red Blood Cells (×10^{12}/L)	4.80 (4.50-5.00)	4.80 (4.50-5.00)	4.73±0.40	-0.013	0.990
Hemoglobin (g/L)	135.53±15.02	135.37±15.34	136.86±12.21	0.592	0.557
Hematocrit (%)	41.19±5.00	41.36±4.95	39.79±5.33	-1.482	0.148
Platelets (×10^9/L)	236.68±38.33	236.27±38.75	240.14±35.12	0.545	0.589
Urea (mmol/L)	4.95±1.00	4.96±1.02	4.95 (4.52-5.38)	-0.290	0.772
Serum Creatinine (μmol/L)	80.79±11.95	80.64±12.01	82.03±11.49	0.602	0.551
Uric Acid (μmol/L)	339.84±100.79	339.56±98.32	342.18±121.56	0.110	0.913
Creatine Kinase (U/L)	93.09±30.57	93.89±30.79	86.39±28.32	-1.312	0.198
Lactate Dehydrogenase (U/L)	190.47±26.56	191.47±26.16	182.07±28.82	-1.647	0.109
Creatine Kinase-MB (U/L)	18.00 (16.00-21.00)	18.00 (16.00-21.00)	20.00 (15.00-21.00)	0.918	0.357
Prothrombin Time (seconds)	11.00 (10.70-11.40)	11.00 (10.70-11.40)	11.00±0.39	-0.335	0.738
International Normalized Ratio (INR)	0.94±0.08	0.94±0.08	0.95±0.08	0.669	0.508
Fibrinogen (g/L)	3.02±0.51	3.03±0.52	2.92±0.36	-1.480	0.146
Thrombin Time (seconds)	16.47±1.95	16.44±1.98	16.72±1.64	0.846	0.403
Activated Partial Thromboplastin Time (seconds)	25.20±1.70	25.14±1.67	25.69±1.92	1.442	0.159
Pre-treatment NIHSS score	11.00 (10.00-12.00)	11.00 (10.00-12.00)	10.50 (10.00-11.00)	-1.034	0.285
Post-treatment NIHSS score	3.50 (3.00-5.00)	3.00 (3.00-5.00)	5.00 (4.75-6.00)	2.689	0.005
Pre-treatment mRS score	3.00 (3.00-3.00)	3.00 (3.00-3.00)	3.00 (3.00-3.00)	-0.842	0.074
Post-treatment mRS score	1.00 (1.00-2.00)	1.00 (1.00-2.00)	2.00 (2.00-2.00)	4.085	< 0.001
Pre-treatment BDNF (μg/L)	7.99±2.07	8.04±2.08	7.54±1.95	-1.289	0.206
Post-treatment BDNF (μg/L)	13.12±3.98	13.24±3.95	12.07±4.08	-1.448	0.157
Pre-treatment NSE (U/L)	56.24±4.04	56.24±4.01	56.24±4.40	-0.001	0.999

Post-treatment NSE (U/L)	26.35 (23.55-29.52)	26.20 (23.48-29.23)	27.71±3.87	1.255	0.210
Pre-treatment PAF (pg/mL)	97.93±19.12	98.17±19.41	95.87±16.66	-0.677	0.503
Post-treatment PAF (pg/mL)	70.75 (61.12-81.30)	69.34±14.22	92.92±14.17	8.318	< 0.001
Pre-treatment hs-CRP (mg/L)	12.68±2.16	12.71±2.13	12.46±2.40	-0.519	0.607
Post-treatment hs-CRP (mg/L)	4.96 (4.14-9.21)	4.76 (4.05-9.05)	8.84 (6.67-9.73)	3.106	0.002
Pre-treatment Hcy (μmol/L)	22.55±2.16	22.56±2.18	22.43±1.98	-0.323	0.749
Post-treatment Hcy (μmol/L)	15.43 (13.87-18.82)	15.11 (13.75-18.60)	19.90 (16.23-21.11)	5.311	< 0.001
Pre-treatment IL-1β (mg/L)	32.52±4.56	32.52±4.51	32.50±4.99	-0.02	0.984
Post-treatment IL-1β (mg/L)	18.05 (15.90-21.45)	17.38 (15.81-21.19)	20.23±3.05	3.072	0.002

Note: BMI, Body Mass Index; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; BDNF, Brain-Derived Neurotrophic Factor; NSE, Neuron-Specific Enolase; PAF, Platelet-Activating Factor; hs-CRP, High-sensitivity C-reactive Protein; Hcy, Homocysteine; IL-1β, Interleukin-1β.

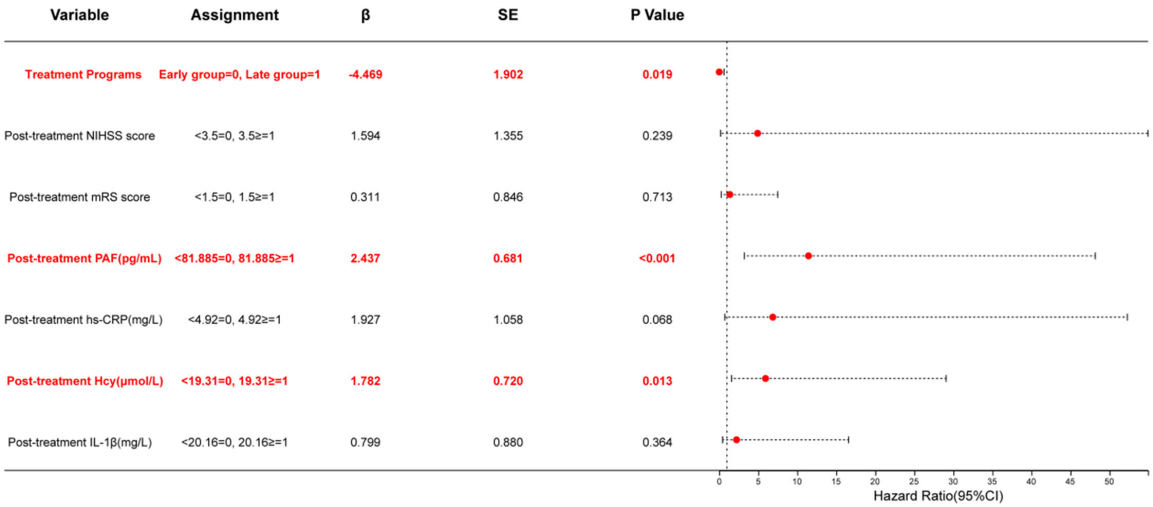

Figure 7. Multivariate logistic regression analysis. Note: NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; BDNF, Brain-Derived Neurotrophic Factor; NSE, Neuron-Specific Enolase; PAF, Platelet-Activating Factor; hs-CRP, High-sensitivity C-reactive Protein; Hcy, Homocysteine; IL-1β, Interleukin-1β.

effects of early tirofiban use in diverse patient populations.

Based on the results, future studies should investigate the long-term prognostic impact of tirofiban administration at different time windows in acute ischemic stroke. The combined therapeutic effects of tirofiban with other antiplatelet or anticoagulant drugs also warrant exploration, particularly in complex cases. Conducting multi-center, large-sample, prospective randomized controlled trials is crucial to validating the safety and efficacy of early tirofiban use and optimizing treatment strategies for acute ischemic stroke. Given the importance of PAF and Hcy in treatment outcomes, future research should also evaluate the potential of these biomarkers in predicting treatment efficacy.

In summary, this study demonstrated that early administration of tirofiban in the treatment of acute ischemic stroke offers significant clinical advantages, including improved neurological function, enhanced daily living ability, and reduced inflammatory responses and complications. These findings provide new evidence for the clinical application of tirofiban, supporting its use within 6 hours after thrombolysis to optimize treatment outcomes and improve patient prognosis. Future research should continue to explore the application of tirofiban in diverse patient populations to further refine treatment strategies for acute ischemic stroke.

Disclosure of conflict of interest

None.

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