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Original Article

Effect of tirofiban arterial injection on neurological and endothelial function in acute ischemic stroke patients beyond the thrombolysis time window

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Abstract: Objective: To evaluate the efficacy and safety of arterial tirofiban injection in patients with acute ischemic stroke (AIS) beyond the thrombolysis time window. Methods: In this retrospective single-center study, clinical data were analyzed from 230 AIS patients treated at the First Hospital of Yulin between July 2021 and January 2023. Patients were divided into two groups: the observation group (n=102) treated with tirofiban combined with dual antiplatelet therapy, and the control group (n=128) that received dual antiplatelet therapy alone. Post-treatment follow-up evaluated neurological function, endothelial function, and safety using the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Barthel Index (BI). Endothelial function was assessed by measuring levels of endothelin-1 (ET-1), nitric oxide (NO), and von Willebrand factor (vWF). Baseline characteristics, treatment protocols, and complications were analyzed to ensure the reliability and scientific rigor of the results. Results: Compared to the control group, the observation group demonstrated significant improvements in NIHSS, mRS, and BI scores, indicating enhanced neurological function and self-care ability. Endothelial markers (ET-1, NO, and vWF) also significantly improved in the observation group, suggesting a beneficial effect on endothelial function. The overall efficacy rate at 90 days was 86.72% in the observation group, significantly higher than the 74.50% in the control group ($P<0.05$). In terms of safety, there were no significant differences in the incidence of adverse events between the two groups, indicating that tirofiban is well-tolerated. Multivariate analysis identified age, treatment protocol, and baseline NO levels as independent factors affecting the 90-day prognosis, underscoring the importance of individualized treatment strategies for AIS patients. Conclusion: Arterial injection of tirofiban significantly improves neurological and endothelial function in AIS patients beyond the thrombolysis time window while maintaining a favorable safety profile. These findings support the use of tirofiban in patients who are ineligible for intravenous thrombolysis or endovascular treatment.

Keywords: Tirofiban, acute ischemic stroke, neurological function, endothelial function, thrombolysis, safety

Introduction

In 2019, epidemiological data reported 3.94 million new stroke cases in China, representing an 86% increase in incidence compared to 1990, with 2.87 million of these cases being ischemic strokes [1]. Additionally, the affected population is becoming younger. Acute ischemic stroke (AIS) is the most prevalent type of stroke in China, accounting for 69.6% to 70.8% of all stroke cases. AIS is characterized by high disability rates, high incidence, and high mortality [2]. It occurs when blood flow to the brain is suddenly reduced or interrupted, leading to ischemic and hypoxic necrosis of localized brain cells. This results in a series of neurological dysfunctions that severely impact patients' quality of life, making AIS one of the leading causes of death and disability among Chinese adults [3]. Consequently, improving the prognosis of AIS has become a key focus in current medical research.

The treatment time window for AIS is critical. Intravenous thrombolysis (IVT) with alteplase (rt-PA) administered within 4.5 hours of symptom onset is the standard and preferred method for achieving significant short-term efficacy

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[4-6]. However, despite meeting treatment criteria, only 18.3% of patients receive IVT, and among those treated, only 30% achieve a favorable prognosis [7, 8]. Many patients miss the thrombolysis time window due to factors such as delayed hospital arrival, often caused by transportation challenges, residing in remote areas, or failing to recognize symptoms promptly. Additionally, some patients may initially present with mild symptoms, delaying AIS recognition until the condition worsens, or they may have limited access to medical resources in certain regions. Furthermore, contraindications like advanced age, severe hypertension, or increased bleeding risk can render some patients ineligible for rt-PA treatment. For patients beyond the thrombolysis time window, endovascular therapy (EVT) has emerged as an alternative treatment, involving the removal or disruption of thrombi to restore cerebral blood flow and reduce ischemic brain damage [9-11]. However, for some patients who do not meet the criteria for mechanical thrombectomy or stenting, traditional oral antiplatelet drugs have limited effectiveness due to their slow action and potential for drug resistance [12]. Therefore, identifying effective treatment options for AIS patients who fall outside the standard time window remains a significant challenge.

Tirofiban is a platelet glycoprotein (GP) IIb/IIIa receptor inhibitor that prevents fibrinogen from binding to platelet GP IIb/IIIa receptors, thereby inhibiting platelet aggregation [12]. It is highly effective, has a short half-life, and was initially used to treat acute coronary syndrome, demonstrating significant efficacy during percutaneous coronary intervention (PCI) [13]. In recent years, tirofiban has gradually been introduced for the treatment of cerebrovascular diseases, particularly in AIS management. Studies suggest that tirofiban can effectively reduce the risk of thrombus reformation after arterial recanalization by inhibiting platelet aggregation, thereby improving patient prognosis. Moreover, tirofiban has gained preliminary recognition for its application in combination with IVT and EVT, showing favorable efficacy and safety profiles [14-16]. Currently, tirofiban is included as a potential drug for AIS treatment in Chinese guidelines. However, despite its demonstrated effectiveness, further research is needed to determine the optimal dosing and administration methods due to limited study samples [17].

This study aims to investigate the application of arterial tirofiban injection in AIS patients beyond the thrombolysis time window. By comparing National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Barthel Index (BI) scores, as well as adverse events, between two groups before and after treatment, this research seeks to evaluate the efficacy and safety of tirofiban. The findings aim to provide evidence-based support for the treatment of AIS patients beyond the standard time window.

Methods and materials

Study subjects

This single-center, retrospective case-control study aimed to evaluate the efficacy and safety of arterial tirofiban injection in AIS patients beyond the thrombolysis time window.

Sample information

This study was conducted on 230 AIS patients treated at The First Hospital of Yulin between July 2021 and January 2023. Patients who received sequential dual antiplatelet therapy with tirofiban were assigned to the observation group (n=102), while those who received only dual antiplatelet therapy were assigned to the control group (n=128). This study was approved by the Ethic Committee of The First Hospital of Yulin.

Inclusion and exclusion criteria

Inclusion criteria: patients meeting AIS diagnostic criteria [18], with onset time between 6 and 24 hours; patients who underwent digital subtraction angiography (DSA) confirming the absence of severe stenosis or occlusion in major intracranial or extracranial vessels. Exclusion criteria: patients who had received intravenous thrombolysis; those with severe organ dysfunction; platelet count below 100×10^9/L; or presence of other bleeding tendencies.

Grouping and treatment methods

Patients in the control group underwent DSA examination to identify the responsible vessel

and were subsequently administered dual antiplatelet therapy. This regimen included enteric-coated aspirin tablets (manufacturer: Bayer, batch number: asp100) and clopidogrel hydrogen sulfate tablets (manufacturer: Sanofi, batch number: clop75). Dual antiplatelet therapy was continued for 21 days, followed by monotherapy with either enteric-coated aspirin or clopidogrel hydrogen sulfate tablets for an additional 90 days.

Patients in the observation group also underwent DSA examination to identify the responsible vessel. Patients received an arterial injection of 8-10 ml (0.4-0.5 mg) of tirofiban hydrochloride sodium chloride injection (manufacturer: Yuanda Pharmaceutical, batch number: ml024102), followed by a 24-hour intravenous infusion of tirofiban. Subsequently, these patients received the same dual antiplatelet therapy regimen as the control group, consisting of 21 days of dual antiplatelet therapy followed by 90 days of monotherapy with either enteric-coated aspirin or clopidogrel hydrogen sulfate tablets.

Data collection

Data collected included general demographic information (age, gender), medical history (e.g., hypertension, diabetes, history of cerebral infarction), NIHSS, mRS, and BI scores before and after treatment, endothelial function indicators (ET-1, NO, and vWF), as well as hemoglobin (g/L), triglycerides (mmol/L), high-density lipoprotein (HDL, mmol/L), and low-density lipoprotein (LDL, mmol/L). Adverse events (e.g., bleeding, thrombocytopenia) during treatment and patient outcomes were also recorded.

Detection methods

Endothelial function indicators were measured by collecting peripheral blood from patients before treatment and 90 days after treatment, using enzyme-linked immunosorbent assay (ELISA) kits provided by Shanghai Enzyme-linked Biotechnology.

Functional scores

NIHSS: Used NIHSS was used to evaluate the severity of neurological impairment, with scores ranging from 0 to 42, where higher scores indicate greater neurological impairment [19]. Treatment efficacy was assessed based on changes in NIHSS scores before and after treatment. Efficacy was categorized as follows: Cure (reduction of 91%-100%), Marked effective (reduction of 46%-90%), Effective (reduction of 18%-45%), and Ineffective (reduction or increase of less than 17%, deterioration: increase of more than 18%, or death). The total efficacy rate was calculated as: (Cure + Marked effective + Effective) cases/Total cases × 100%.

The mRS was used to assess functional independence, with scores ranging from 0 to 6, where 0 indicates no symptoms and 6 indicates death. Higher scores indicate greater functional impairment. A post-treatment mRS score ≤2 indicates a favorable prognosis, while >2 indicates an unfavorable prognosis [20].

The BI was used to assess the patient's ability to perform activities of daily living, with scores ranging from 0 to 100, where higher scores indicate better self-care ability [21]. All scores except NIHSS were assessed 90 days post-treatment, while NIHSS was assessed 7 days post-treatment.

Outcome measures

The primary outcomes included neurological function improvement assessed by NIHSS, functional independence assessed by mRS, self-care ability assessed by BI, and improvement in endothelial function indicators (ET-1, NO, vWF). The secondary outcomes included the incidence of adverse events occurring within 90 days in both groups, such as bleeding and thrombocytopenia, to evaluate the safety of tirofiban.

Statistical analysis

Data were analyzed using SPSS 26.0 software. Continuous variables with a normal distribution were expressed as mean ± standard deviation, and comparisons between groups were conducted using the independent samples t-test. Continuous variables with a non-normal distribution were expressed as median and interquartile range and compared using the Mann-Whitney U test. Categorical variables were expressed as percentages, and comparisons between groups were conducted using the chi-square (χ^2) test. Logistic regression analysis

Table 1. Comparison of baseline characteristics between the two groups of patients

Variable	Observation group (n=128)	Control group (n=102)	Statistic Value	*P* Value
Age	62.63±10.32	62.57±9.14	-0.044	0.965
Gender				
Male	91 (71.09%)	66 (64.71%)	1.069	0.301
Female	37 (28.91%)	36 (35.29%)		
Disease Type				
Ischemic Stroke	27 (21.09%)	24 (23.53%)	0.195	0.659
Transient Ischemic Attack	101 (78.91%)	78 (76.47%)		
Intracerebral Hemorrhage				
Yes	10 (7.81%)	5 (4.90%)	0.789	0.374
No	118 (92.19%)	97 (95.10%)		
Hypertension				
Yes	73 (57.03%)	55 (53.92%)	0.222	0.637
No	55 (42.97%)	47 (46.08%)		
Diabetes				
Yes	26 (20.31%)	30 (29.41%)	2.552	0.110
No	102 (79.69%)	72 (70.59%)		
Coronary Heart Disease				
Yes	6 (4.69%)	9 (8.82%)	1.593	0.207
No	122 (95.31%)	93 (91.18%)		
Hyperlipidemia				
Yes	64 (50%)	56 (54.90%)	0.547	0.460
No	64 (50%)	46 (45.10%)		
Smoking History				
Yes	41 (32.03%)	42 (41.18%)	2.058	0.151
No	87 (67.97%)	60 (58.82%)		
Alcohol History				
Yes	23 (17.97%)	17 (16.67%)	0.067	0.796
No	105 (82.03%)	85 (83.33%)		
Hemoglobin (g/L)	148.00±10.03	147.05±10.03	-0.710	0.478
Triglycerides (mmol/L)	1.32±0.49	1.29±0.51	-0.417	0.677
HDL (mmol/L)	1.19±0.38	1.12±0.29	-1.421	0.157
LDL (mmol/L)	3.24±0.99	3.33±1.14	0.647	0.519

Note: HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein.

was used to identify independent risk factors affecting the 90-day prognosis. A *P*-value of <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between the two groups

A comparison of baseline characteristics between the observation group (n=102) and the control group (n=128) revealed no significant differences across all variables (all P>0.05, **Table 1**). The specific *P*-values are as follows: age (P=0.965), gender distribution (P=0.301), disease type (P=0.659), cerebral hemorrhage (P=0.374), hypertension (P=0.637), diabetes (P=0.11), coronary heart disease (P=0.207), hyperlipidemia (P=0.460), smoking history (P=0.151), drinking history (P=0.796), hemoglobin (P=0.478), triglycerides (P=0.677), HDL (P=0.157), and LDL (P=0.519).

Changes in endothelial function indicators

Before treatment, there were no significant differences in endothelial function indicators (ET-1, NO, vWF) between the observation and con-

Table 2. Comparison of endothelial indicators between the two groups before and after treatment

Variables	Observation group (n=128)	Control group (n=102)	Statistic Value	*P* Value
Before treatment ET-1 (μg/L)	81.99±5.97	83.00±6.28	-1.233	0.219
After treatment ET-1 (μg/L)	32.01±5.27*	51.99±6.09*	-26.240	<0.001
Before treatment NO1 (μmol/L)	46.08±6.35	45.79±6.70	0.336	0.737
After treatment NO1 (μmol/L)	67.03±7.30*	51.46±7.14*	16.257	<0.001
Before treatment vWF (μg/L)	208.19±32.60	206.59±34.86	0.355	0.723
After treatment vWF (μg/L)	121.39±36.19*	159.01±35.58*	-7.906	<0.001

Note: *P<0.05, compare with before treatment. ET-1, Endothelin-1; NO, Nitric Oxide; vWF, von Willebrand factor.

Table 3. Comparison of functional scores between the two groups before and after treatment

Functional score	Observation group (n=128)	Control group (n=102)	Statistic Value	*P* Value
Before treatment NIHSS	5.00 [3.00, 7.00]	5.00 [3.00, 8.00]	-0.797	0.423
After treatment NIHSS	2.00 [1.00, 2.00]*	2.00 [2.00, 3.00]*	-3.938	<0.001
Before treatment mRS	3.00 [2.00, 4.00]	3.00 [3.00, 3.00]	0.615	0.504
After treatment mRS	1.00 [0.00, 1.00]*	2.00 [1.00, 3.00]*	-5.576	<0.001
Before treatment BI	85.00 [73.75, 100.00]	95.00 [76.25, 100.00]	-1.173	0.221
After treatment BI	95.00 [90.00, 100.00]*	95.00 [85.00, 95.00]*	3.148	0.001

Note: *P<0.05, compared with before treatment. NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index.

trol groups (all P>0.050). After treatment, significant improvements were observed in both groups. Specifically, the ET-1 level in the observation group significantly decreased post-treatment, with a greater reduction compared to the control group (P<0.001). The NO level significantly increased in the observation group, surpassing the increase in the control group (P<0.001). Additionally, the vWF level significantly decreased in the observation group, showing a significant difference compared to the control group (P<0.001). Detailed results are shown in **Table 2**.

Comparison of functional scores between the two groups

Prior to treatment, there were no significant differences in NIHSS, mRS, and BI scores between the observation and control groups (P>0.050). Post-treatment assessments revealed significant improvements in both groups. Specifically, the NIHSS score and mRS score in the observation group significantly decreased, which were lower than the control group (both P<0.001), indicating better neurological function and independence compared to the control group. Furthermore, the BI score significantly increased in the observation group, higher than that in the control group (P=0.001), reflecting enhanced self-care ability. Detailed scores are provided in **Table 3**.

Comparison of overall efficacy after treatment between the two groups

Based on the NIHSS score, the overall efficacy rate after treatment was significantly higher in the observation group (86.72%) compared to the control group (74.50%, P=0.018) (**Table 4**). Specifically, the cure rate in the observation group was 7.81%, the marked effective rate was 57.03%, the effective rate was 21.88%, and the ineffective rate was 13.28%. In the control group, the cure rate was 6.86%, the marked effective rate was 56.86%, the effective rate was 10.78%, and the ineffective rate was 25.50%.

Comparison of 90-day prognosis between the two groups

At 90 days post-treatment, the good prognosis rate, as assessed by the mRS score, was significantly higher in the observation group (90.63%) compared to the control group (72.55%, P<0.001) (**Table 5**). Specifically, 116 patients in the observation group achieved a good prognosis, while 12 had a poor prognosis. In contrast, 74 patients in the control group had

Table 4. Comparison of overall treatment efficacy between the two groups after treatment

	Cured	Significantly effective	Effective	Ineffective	Overall effective rate
Observation Group (n=128)	10 (7.81%)	73 (57.03%)	28 (21.88%)	17 (13.28%)	110 (86.72%)
Control Group (n=102)	7 (6.86%)	58 (56.86%)	11 (10.78%)	26 (25.50%)	76 (74.50%)
Statistic Value					5.566
P Value					0.018

Table 5. Comparison of 90-day prognostic outcome between the two groups

	Good prognosis	Poor prognosis
Observation Group (n=128)	116	12
Control Group (n=102)	74	28
Statistic Value	12.910	
P Value	<0.001	

a good prognosis, and 28 had a poor prognosis.

Comparison of adverse events between the two groups

There were no significant differences in the incidence of adverse events between the observation and control groups (P>0.050). Specifically, gastrointestinal bleeding occurred in 2.34% of the observation group versus 1.96% of the control group (P=0.843). Hematuria occurred in 0.78% of the observation group compared to 0.98% of the control group (P=0.872). Allergic reactions were observed in 0.78% of the observation group and 0% of the control group (P=0.371). Thrombocytopenia occurred in 2.34% of the observation group versus 1.96% of the control group (P=0.843). Fever was reported in 0.78% of the observation group and 0.98% of the control group (P=0.872). The total incidence of adverse events was 7.03% in the observation group and 5.88% in the control group (P=0.726). Detailed adverse event data are shown in **Table 6**.

Univariate analysis of factors affecting 90-day prognosis

Univariate analysis was performed on various variables, including demographic factors (e.g., age, gender), comorbidities (e.g., hypertension, diabetes, coronary heart disease), lifestyle factors (e.g., smoking and drinking history), and baseline clinical and biochemical indicators (e.g., NIHSS, BI, NO, ET-1, vWF). The analysis identified age (P<0.001), hypertension (P= 0.006), treatment regimen (P<0.001), pre-treatment NIHSS score (P=0.044), and pre-treatment NO level (P<0.001) as factors significantly associated with the 90-day prognosis. Detailed results are presented in **Table 7**.

Multivariate analysis of factors affecting 90-day prognosis

First, we assigned values (**Table 8**) to the indicators with univariate differences. Variables with a *P*-value <0.050 in the univariate analysis (age, hypertension, treatment regimen, pre-treatment NIHSS score, and pre-treatment NO level) were included in the multivariate logistic regression analysis. This analysis revealed that the treatment regimen (OR=4.216, P=0.001, 95% CI: 1.790-10.550), age (OR=14.290, P< 0.001, 95% CI: 5.491-43.673), and pre-treatment NO level (OR=0.190, P<0.001, 95% CI: 0.074-0.452) were independent factors affecting the 90-day prognosis. Hypertension (P=0.159) and pre-treatment NIHSS score (P=0.128) were not significantly associated with prognosis in the multivariate analysis. Detailed findings are illustrated in **Figure 1**.

Based on ROC curve analysis, treatment regimen, age, hypertension, pre-treatment NIHSS score, and pre-treatment NO level demonstrated varying degrees of discriminative ability in predicting the 90-day prognosis. Age had the highest area under the curve (AUC=0.851), followed by pre-treatment NO level (AUC=0.672), pre-treatment NIHSS score (AUC=0.661), treatment regimen (AUC=0.655), and hypertension had the lowest AUC (0.620). In terms of sensitivity, age was the highest (87.40%), whereas pre-treatment NO level was the lowest (57.50%). For specificity, age and pre-treatment NO level were relatively high (73.70%), while hypertension had the lowest specificity (48.90%). Detailed ROC analysis is presented in **Figure 2**.

Table 6. Comparison of adverse events between the two groups

Adverse events	Observation group (n=128)	Control group (n=102)	Statistic Value	*P* Value
Gastrointestinal Bleeding	3 (2.34%)	2 (1.96%)	0.039	0.843
Hematuria	1 (0.78%)	1 (0.98%)	0.026	0.872
Allergy	1 (0.78%)	0 (0%)	0.800	0.371
Thrombocytopenia	3 (2.34%)	2 (1.96%)	0.039	0.843
High Fever	1 (0.78%)	1 (0.98%)	0.026	0.872
Total Incidence Rate	9 (7.03%)	6 (5.88%)	0.123	0.726

Table 7. Univariate analysis of factors affecting 90-day prognosis in patients

Variables	Poor prognosis group (n=40)	Good prognosis group (n=190)	Statistic Value	*P* Value
Age	74.00 [66.00, 77.25]	61.00 [55.00, 66.00]	6.971	<0.001
Gender				
Male	29 (72.5%)	128 (67.37%)	0.402	0.526
Female	11 (27.5%)	62 (32.63%)		
Disease Type				
Ischemic Stroke	8 (20%)	43 (22.63%)	0.133	0.716
Transient Ischemic Attack	32 (80%)	147 (77.37%)		
Intracerebral Hemorrhage				
Yes	1 (2.5%)	14 (7.37%)	1.285	0.257
No	39 (97.5%)	176 (92.63%)		
Hypertension				
Yes	30 (75%)	97 (51.05%)	7.663	0.006
No	10 (25%)	93 (48.95%)		
Diabetes				
Yes	12 (30%)	44 (23.16%)	0.840	0.359
No	28 (70%)	146 (76.84%)		
Coronary Heart Disease				
Yes	2 (5%)	13 (6.84%)	0.184	0.668
No	38 (95%)	177 (93.16%)		
Hyperlipidemia				
Yes	22 (55%)	98 (51.58%)	0.155	0.694
No	18 (45%)	92 (48.42%)		
Smoking History				
Yes	16 (40%)	67 (35.26%)	0.321	0.571
No	24 (60%)	123 (64.74%)		
Alcohol History				
Yes	7 (17.5%)	33 (17.37%)	<0.001	0.984
No	33 (82.5%)	157 (82.63%)		
Treatment Plan				
Dual Antiplatelet Therapy + Tirofiban Group	28 (70%)	74 (38.95%)	12.910	<0.001
Dual Antiplatelet Therapy Group	12 (30%)	116 (61.05%)		
Hemoglobin (g/L)	147.21±10.10	148.75±9.65	-0.886	0.377
Triglycerides (mmol/L)	1.33±0.51	1.21±0.42	1.401	0.163
HDL (mmol/L)	1.15±0.33	1.16±0.37	-0.181	0.857
LDL (mmol/L)	3.33±1.09	3.09±0.96	1.296	0.196
Before treatment NIHSS	5.00 [3.00, 7.00]	6.00 [4.00, 9.00]	2.016	0.044

Before treatment BI	90.00 [70.00, 100.00]	95.00 [80.00, 100.00]	0.901	0.368
Before treatment ET-1 (μg/L)	82.27±6.22	83.25±5.58	-0.921	0.358
Before treatment NO1 (μmol/L)	46.63±6.44	42.77±5.85	3.499	<0.001
Before treatment vWF (μg/L)	206.75±33.65	210.92±33.29	-0.714	0.476

Note: HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; ET-1, Endothelin-1; NO, Nitric Oxide; vWF, von Willebrand factor; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index.

Table 8. Assignment table

Factor	Type of variable	Assignment content
Treatment plan	(X)	Dual Antiplatelet Therapy + Tirofiban Group =1, Dual Antiplatelet Therapy Group =2
Age	(X)	≥64.5=1, <64.5=2
Hypertension	(X)	Yes =1, No =2
Before NIHSS	(X)	≥6.5=1, <6.5=2
Before NO-1	(X)	≥44.525=1, <44.525=2
Prognosis	(Y)	Poor =1, Good =2

Note: NO, Nitric Oxide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

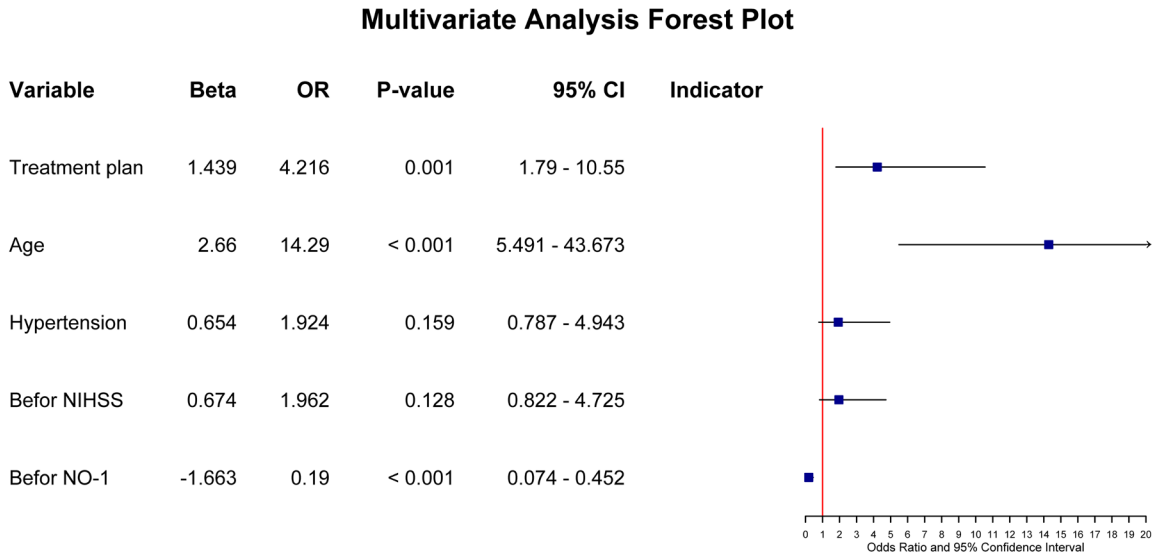

Figure 1. Multivariate logistic analysis of factors affecting 90-day prognosis in patients. Note: NO, Nitric Oxide; NIHSS, National Institutes of Health Stroke Scale.

Discussion

This study found that intra-arterial injection of tirofiban significantly improved clinical outcomes compared to the control group in patients with AIS. Specifically, patients in the treatment group exhibited significant improvements in NIHSS, mRS, and BI scores, indicating enhanced neurological function and self-care ability. Additionally, endothelial function markers - such as ET-1, NO, and vWF - improved significantly in the treatment group compared to the control group, underscoring the beneficial effects of tirofiban on vascular health. These results suggest that tirofiban is effective for AIS patients even beyond the thrombolysis time window, offering a viable treatment alternative for patients who miss the window for conventional thrombolysis. In line with our findings, Liu et al. [22] demonstrated the neuroprotective effects of tirofiban in AIS by reducing neuroinflammation, while Kang et al. [23] reported significant improvements in endothelial function in acute myocardial infarction patients.

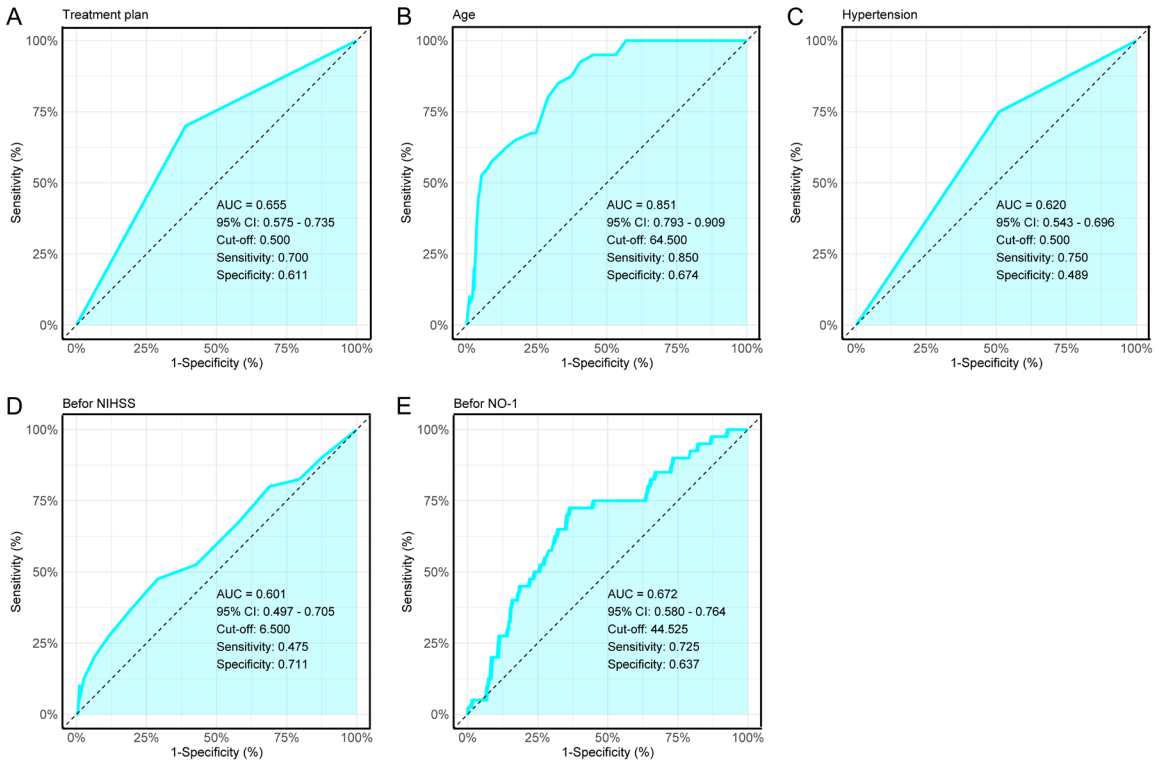

Figure 2. ROC curves of significant risk factors in predicting 90-day prognosis in patients. A: Treatment Plan (AUC=0.685, 95% CI: 0.579-0.736, Cut-off =0.730, Sensitivity =0.700, Specificity =0.611); B: Age (AUC=0.851, 95% CI: 0.759-0.905, Cut-off =68.5, Sensitivity =0.789, Specificity =0.874); C: Hypertension (AUC=0.603, 95% CI: 0.553-0.695, Cut-off =0.690, Sensitivity =0.750, Specificity =0.489); D: NIHSS before treatment (AUC=0.641, 95% CI: 0.607-0.705, Cut-off =6.00, Sensitivity =0.743, Specificity =0.711); E: NO1 before treatment (AUC=0.672, 95% CI: 0.569-0.764, Cut-off =44.6, Sensitivity =0.765, Specificity =0.537). Note: NO, Nitric Oxide; NIHSS, National Institutes of Health Stroke Scale.

Similarly, Cho et al. [24] showed the safety and efficacy of low-dose intra-arterial tirofiban in patients with a large ischemic core, further supporting its clinical relevance in AIS treatment.

Tirofiban, a platelet glycoprotein IIb/IIIa receptor inhibitor, has increasingly been utilized for treating cerebrovascular diseases in recent years [25]. While its efficacy in acute coronary syndrome as an adjunct during PCI is well-established, emerging small-sample studies have highlighted its potential efficacy and safety in AIS. Building upon this research, our study specifically investigated the use of tirofiban in AIS patients who miss the thrombolysis time window. The results indicate that tirofiban significantly improves both neurological and endothelial functions, further supporting its potential as a treatment option in cerebrovascular diseases. Compared to traditional IVT and EVT, tirofiban offers effectiveness over a longer therapeutic window, making it a viable alternative for patients beyond the thrombolysis window. Importantly, intra-arterial administration ensures high local drug concentrations, which enhances efficacy while minimizing systemic side effects. These findings are consistent with the previous literature; Ribeiro et al. [26] reported differences in endothelial function between left and right hemisphere stroke patients, while Filchenko et al. [27] emphasized the importance of blood pressure variability and endothelial function in stroke prognosis, supporting tirofiban as an effective treatment for AIS patients. Additionally, Li et al. [28] demonstrated that tirofiban combined with EVT significantly improved functional outcomes in AIS patients.

Tirofiban demonstrated notable advantages in treating AIS. Firstly, it inhibits platelet glycoprotein IIb/IIIa receptor function, preventing fibrinogen binding and effectively inhibiting platelet aggregation and thrombosis [29]. Intra-arterial administration ensures rapid local drug deliv-

ery, providing swift and targeted antithrombotic effects [30]. This study observed a significant decrease in ET-1 levels and an increase in NO levels in the treatment group, indicating improved endothelial function, enhanced blood flow, and better oxygen delivery to brain tissue. Secondly, compared to traditional oral antiplatelet drugs (e.g., aspirin and clopidogrel), tirofiban acts more quickly, making it more effective in acute thrombosis scenarios. Additionally, the results demonstrated better efficacy and reduced neurological impairment in the observation group, even beyond the thrombolysis window. Lin et al. [31] showed that tirofiban combined with tanshinone sodium was more effective than tirofiban alone in treating acute coronary syndrome. Similarly, Du et al. [32] reported significant improvements in neurological function and prognosis when tirofiban was used alongside standard therapy, further supporting its efficacy in AIS treatment.

Univariate and multivariate analyses identified several baseline characteristics that significantly influencing the treatment outcomes of tirofiban. Age, hypertension, treatment strategy, and baseline NO levels were key factors affecting the 90-day prognosis. Age emerged as a particularly important factor, as older patients often have comorbidities, decreased vascular elasticity, and impaired hemodynamic regulation, all of which may lead to poorer treatment outcomes. Additionally, reduced neuroplasticity in elderly patients may hinder recovery. Wu et al. [33] highlighted the strong correlation between age and functional outcomes in ischemic stroke, emphasizing the diminished behavioral recovery seen in older patients. Hypertension was another significant predictor of poor outcomes. Hypertensive patients tend to have damaged vascular endothelium, predisposing them to thrombosis and vascular remodeling, both of which can impair cerebral perfusion and response to treatment. Moreover, hypertension may exacerbate blood-brain barrier dysfunction and inflammation following stroke, further worsening prognosis. Ma et al. [34] demonstrated that hypertension significantly impacts ischemic stroke prognosis and recurrence, particularly when evaluated alongside lipid markers. The treatment strategy also played a crucial role; intra-arterial tirofiban maintains high local drug concentrations, enhancing efficacy while minimizing systemic side effects, making it a suitable option for patients beyond the intravenous thrombolysis (IVT) window. Szmygin et al. [35] found that recanalization outcomes in posterior circulation stroke patients were closely associated with baseline NIHSS scores and reperfusion time, underscoring the importance of optimizing treatment strategies. Higher baseline NO levels, indicative of better endothelial function, were correlated with a more favorable prognosis. As an important marker of endothelial function, NO promotes vasodilation and improves cerebral blood flow, aiding neurological recovery. Chang et al. [36] showed that cardiac biomarkers, such as NT-proBNP and LDH, are significantly associated with poor clinical outcomes in ischemic stroke, highlighting the critical role of endothelial function in stroke prognosis. Analyzing these baseline characteristics provides valuable insights into optimizing treatment strategies and selecting appropriate patient populations. Elderly patients and those with hypertension may require more aggressive, individualized treatment to improve outcomes.

In terms of safety, no significant differences in adverse events were observed between the tirofiban treatment and control groups. The incidence of gastrointestinal bleeding, hematuria, and thrombocytopenia did not differ significantly between the groups, indicating that tirofiban is safe in this clinical context. Specifically, intra-arterial tirofiban did not increase the risk of systemic side effects, while still maintaining local efficacy, further supporting its safety profile. Zhao et al. [37] reported that intravenous tirofiban did not significantly increase the risk of bleeding in non-cardiogenic patients, and Filchenko et al. [27] also confirmed the safety of tirofiban. Compared to traditional oral antiplatelet drugs, tirofiban provides rapid antiplatelet effects without significantly increasing the incidence of adverse reactions. This makes tirofiban particularly suitable for patients who are unable to take oral medications or those with swallowing difficulties. These findings reinforce the use of tirofiban in AIS patients, particularly during the acute phase when prompt antiplatelet action is crucial.

Study limitations and clinical implications

Despite the positive findings, this study has several limitations. As a single-center, retro-

spective study with a small sample size, it may be subject to selection bias, which could affect the generalizability of the results. Controlling for factors such as patient adherence and the severity of comorbidities proved challenges and may have influenced the outcomes. Additionally, the 90-day follow-up period limited the ability to assess the long-term outcomes of tirofiban treatment. Future studies should include large-scale, multicenter prospective randomized controlled trials to validate the long-term efficacy and safety of tirofiban in AIS. Additionally, investigations into the combined effects of tirofiban with other antiplatelet agents and its potential use in different AIS subtypes are warranted. In conclusion, tirofiban significantly improves neurological and endothelial functions while maintaining a favorable safety profile, providing a promising treatment option for AIS patients ineligible for timely IVT or mechanical thrombectomy.

Disclosure of conflict of interest

None.

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