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Original Article

Analysis of risk factors for pulmonary infection in acute ischemic stroke patients following intravenous thrombolysis with alteplase

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Abstract: Objective: To identify the risk factors for pulmonary infection in acute ischemic stroke patients treated with intravenous thrombolysis using alteplase. Methods: A retrospective analysis was conducted on 110 acute ischemic stroke patients who received intravenous alteplase thrombolysis between January 2019 and November 2022. The patients were categorized into a pulmonary infection group (40 cases) and a non-infection group (70 cases). Results: Multivariate logistic regression analysis identified the following independent risk factors for pulmonary infection: age, National Institutes of Health Stroke Scale (NIHSS) score at admission, underlying lung disease, hypertension, mechanical ventilation, aspiration, confusion, and elevated C-reactive protein (CRP) levels (all $P<0.05$). The sensitivity and specificity of CRP ifor predicting pulmonary infection were 88.57% and 75.00%, respectively. The NIHSS score demonstrated a sensitivity of 87.14% and a specificity of 70.00%. Further stratification of patients into a good prognosis group (75 cases) and a poor prognosis group (35 cases) revealed that high NIHSS scores at admission, increased fibrinogen (FIB) levels, a thrombolysis window exceeding 3 hours, and concurrent pulmonary infection were independent risk factors for poor prognosis. The area under the ROC curve for NIHSS in predicting prognosis was 0.890, and for FIB, it was 0.854 ($P<0.001$). The sensitivity and specificity of NIHSS for predicting poor prognosis were 89.33% and 82.86%, respectively, while for FIB, they were 84.00% and 82.86%. Conclusions: These findings indicate that factors such as age, NIHSS score, underlying lung disease, hypertension, and elevated CRP levels significantly contribute to the risk of pulmonary infection in acute ischemic stroke patients. Clinicians should closely monitor these values to manage the risk of pulmonary infection effectively.

Keywords: Acute ischemic stroke, alteplase, intravenous thrombolysis, pulmonary infection, risk factors

Introduction

Acute ischemic stroke (AIS) is a prevalent condition, particularly in middle-aged and elderly populations, typically caused by thrombosis in cerebral vessels. This leads to significant vascular stenosis and reduced intracranial blood flow, often resulting in varying degrees of neurological deficits and, in severe cases, can be life-threatening [1, 2]. The primary goal of emergency intravenous thrombolysis is to rapidly restore blood flow in the occluded cerebral vessels, preserve the penumbral tissue surrounding the ischemic core, and mitigate brain injury, thereby enhancing the chances of patient recovery. This therapeutic approach has seen increasing adoption in clinical settings [3]. Recombinant tissue plasminogen activator (rtPA), especially alteplase, is the main thrombolytic agent used globally, with an optimal therapeutic window of 4.5 to 6 hours for effective penumbral salvage [4].

It is important to highlight that while thrombolytic therapy can restore vascular patency, the administration of rtPA is subject to stringent criteria, and the underlying pathophysiology of AIS remains unchanged, which may lead to suboptimal clinical outcomes in some cases [5, 6]. After AIS, patients often experience immune suppression, which lowers their resistance to infections and increases the risk of pulmonary

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complications. This immunosuppressive state is largely due to a prolonged and excessive inflammatory response that depletes immune cell reserves [7, 8]. A subset of AIS patients may develop pulmonary infections following thrombolysis due to multiple factors, presenting with symptoms such as fever and cough. These complications can hinder management, prolong hospital stays, and delay recovery [9]. Therefore, identifying and managing risk factors for post-treatment pulmonary infections in AIS patients is crucial for optimizing clinical outcomes and developing effective prevention strategies.

Currently, there is a lack of personalized predictive studies on the risk factors for pulmonary infections following intravenous thrombolysis with alteplase in AIS patients. This study aims to analyze these risk factors, develop a predictive model, and validate its clinical utility, providing valuable insight for clinical practice.

Materials and methods

Design and overview

A retrospective analysis was conducted on 110 patients with acute ischemic stroke (AIS) who underwent intravenous thrombolysis with alteplase and were admitted to the hospital between January 2019 and November 2022. The patients were categorized into two groups based on the presence of pulmonary infection during hospitalization: a pulmonary infection group (40 cases) and a non-infection group (70 cases). Pulmonary infection was defined by clinical symptoms, including cough, sputum production, fever, chest pain, and dyspnea, along with physical examination findings such as increased and coarse breath sounds or moist rales in the lungs. Laboratory indicators of infection included elevated inflammatory markers, such as increased white blood cell count, neutrophils, or lymphocytes. Chest CT scans showing exudative changes consistent with lung infection were also used for diagnosis [10].

Inclusion criteria: (1) patients diagnosed with AIS and treated with intravenous thrombolysis using alteplase; (2) patients with complete medical and follow-up records.

Exclusion criteria: (1) patients with pre-existing immune system disorders; (2) patients with malignant tumors; (3) patients who did not receive intravenous thrombolysis with alteplase; (4) patients with either acute or chronic infections; (5) patients with a lung infection at the time of admission; (6) patients with mental disorders; (7) patients with severe liver or kidney dysfunction. The study received approval from the ethics committee of Baoji Central Hospital and adhered to the principles outlined in the Declaration of Helsinki.

Thrombolytic therapy

Patients diagnosed with AIS who met the criteria for thrombolysis underwent a series of evaluations, including relevant examinations, comprehensive medical history review, neurological examination, National Institutes of Health Stroke Scale (NIHSS) assessment upon admission [11], and blood tests (routine blood tests, biochemical tests, coagulation function tests, etc.). Intravenous thrombolysis with alteplase was administered at a dose of 0.9 mg/kg (with a maximum dose not exceeding 90 mg). Of the total dose, 10% was given as an intravenous bolus over 1 minute, and the remaining 90% was infused intravenously over 1 hour. If the patient's condition stabilized, a cranial CT was performed 24 hours post-thrombolysis to exclude secondary cerebral hemorrhage, followed by the administration of antiplatelet drugs such as aspirin and clopidogrel. Standard internal medicine treatments were maintained to minimize sample bias.

Outcome measures

Main outcomes: Clinical and pathological characteristics: Comparisons were made between the two groups concerning clinical and pathologic characteristics, including the thrombolysis time window, NIHSS score, presence of pulmonary comorbidities, and history of diabetes.

Laboratory indicators: Laboratory indicators at admission were compared between the two groups, including C-reactive protein (CRP), white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), and coagulation function (D-dimer, fibrinogen (FIB)).

Multifactorial analysis: Logistic multivariate regression analysis was performed to identify

independent risk factors for pulmonary infection following thrombolysis in AIS patients.

Secondary outcomes: Predictive Value Assessment: The predictive value of CRP and NIHSS for pulmonary infection was evaluated. Prognosis Assessment: Prognosis was evaluated 3 months post-treatment using the modified Rankin Scale (mRS) [12], with the following scores: 0: No symptoms; 1 point: No significant disability despite minor symptoms; 2 points: Slight disability; unable to perform previous activities but can handle daily affairs; 3 points: Moderate disability; requiring assistance for daily activities except walking; 4 points: Severe disability; requiring help for daily activities; 5 points: Very severe disability; bedridden, incontinent, requiring constant care; 6 points: Death.

Scores of mRS ≤2 were considered indicative of a good prognosis, while mRS >2 indicated a poor prognosis.

Prognostic analysis: Patients were divided into good prognosis and poor prognosis groups based on their mRS outcomes. Univariate analysis of clinical and pathologic characteristics was conducted, followed by logistic multivariate regression analysis to identify independent factors associated with poor prognosis in AIS patients.

Statistical analysis

Data were processed and analyzed using SPSS 20.0 and GraphPad Prism 8 software. Measured data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and comparisons between groups were conducted using the independent samples t-test. Counted data were expressed as n (%), and analyzed using the chi-square test. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of CRP, WBC, and NIHSS for the occurrence of pulmonary infection. Logistic multivariate regression was employed to determine independent factors influencing pulmonary infection. A *P*-value of <0.05 was considered significant.

Results

Comparison of baseline data

There were no significant differences between the two groups in terms of gender, BMI, drinking history, smoking history, or other baseline characteristics (all P>0.05). However, the proportion of patients aged ≥60 in the lung infection group was significantly higher than in the non-infection group (P<0.05) (**Table 1**).

Comparison of clinical characteristics between the two groups of patients

The pulmonary infection group had a significantly higher proportion of patients with a thrombolysis time window of ≥3 hours, high NIHSS scores, existing lung disease, and hypertension compared to the non-infection group (all P<0.05) (**Table 2**).

Comparison of laboratory indicators between the two groups of patients

We compared CRP, WBC, NEU, LYM, and D-dimer levels between the two groups. The results showed significant differences in CRP, WBC, FIB, and NEU levels (all P<0.05). However, there were no significant differences in LYM, D-dimer, and FIB levels between the two groups (all P>0.05) (**Figure 1**).

Multivariate analysis of pulmonary infection in patients with acute ischemic stroke after intravenous thrombolysis with alteplase

The analysis indicates that several factors, including age, thrombolysis time window, NIHSS score at admission, existing pulmonary disease, concurrent hypertension, mechanical ventilation, aspiration, confusion, and elevated levels of CRP, WBC, and NEU, may contribute to the risk of developing pulmonary infections after thrombolytic therapy. A logistic multivariate regression analysis was performed using pulmonary infection as the dependent variable (coded as 1 for "presence of pulmonary infection"). The independent variables and their corresponding values are presented in **Table 3**. The findings reveal that age, NIHSS score at admission, existing pulmonary disease, concurrent hypertension, mechanical ventilation, aspiration, confusion, and increased CRP levels are independent risk factors for pulmonary infection in stroke patients (all P<0.05) (**Table 4**; **Figure 2**).

Predictive value of CRP and NIHSS scores for pulmonary infection

Elevated CRP and NIHSS scores were identified as independent risk factors for pulmonary

Table 1. Comparison of general conditions between the two groups of patients

Factor	Pulmonary infection group (n = 40)	Non-infection group (n = 70)	χ^2	P
Gender (n, %)			0.005	0.942
Male	22 (55.00)	38 (54.29)		
Female	18 (45.00)	32 (45.71)		
Age (n, %)			0.085	0.770
≥60	24 (60.00)	40 (57.14)		
<60	16 (40.00)	30 (42.86)		
BMI (kg/m^2) (n, %)			0.001	0.971
≥23	21 (52.50)	37 (52.86)		
<23	19 (47.50)	33 (47.14)		
Drinking history (n, %)			0.012	0.914
Yes	19 (47.50)	34 (48.57)		
No	21 (52.50)	36 (51.43)		
Smoking history (n, %)			0.007	0.933
Yes	25 (62.50)	38 (63.33)		
No	15 (37.50)	22 (36.67)		
Family history of stroke (n, %)			0.573	0.449
Yes	17 (42.50)	21 (35.00)		
No	23 (57.50)	39 (65.00)		

Table 2. Comparison of clinical pathological characteristics between the two groups

Factor	Pulmonary infection group (n = 40)	Non-infection group (n = 70)	t/χ^2	P
Thrombolysis time window (n, %)			35.36	<0.001
≥3 h	35 (87.50)	20 (28.57)		
<3 h	5 (12.50)	50 (71.43)		
NIHSS score at admission	15.2±1.71	13.33±1.18		
Underlying lung disease (n, %)			10.61	0.001
Yes	30 (75.00)	30 (42.86)		
No	10 (25.00)	40 (57.14)		
Infarction site (n, %)			0.655	0.418
Anterior circulation	14 (35.00)	30 (42.86)		
Posterior circulation	26 (65.00)	40 (57.14)		
Combined hypertension (n, %)			11.42	0.001
Yes	31 (77.50)	31 (44.29)		
No	9 (22.50)	39 (55.71)		
Mechanical ventilation			10.60	0.001
Yes	30 (75.00)	30 (42.86)		
No	10 (25.00)	40 (57.14)		
Aspiration			12.12	0.005
Yes	25 (65.50)	20 (28.57)		
No	15 (37.50)	50 (71.43)		
Confusion			4.912	0.027
Yes	23 (57.50)	25 (35.71)		
No	17 (42.50)	45 (64.29)		

NIHSS: National Institute of Health stroke scale.

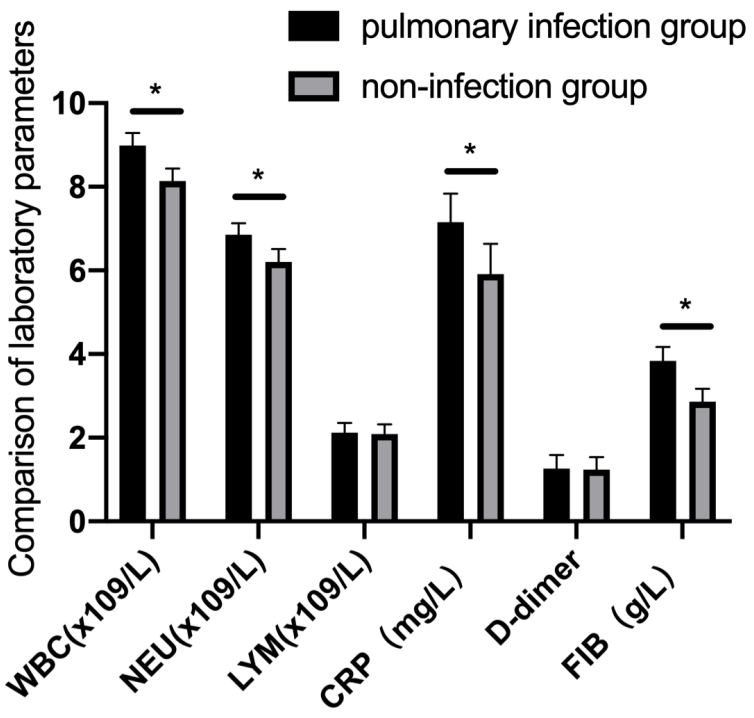

Figure 1. Comparison of laboratory indicators between the two groups of patients. *Indicates P<0.001. CRP: C-reactive protein; WBC: white blood cell count; LYM: lymphocyte count; FIB: fibrinogen; NEU: neutrophil count.

Table 3. Independent variables and their assigned values

Variable	Assigned Value
Age	≥60 = 1, <60 = 0
Thrombolysis time window	≥3 h = 1, <3 h = 0
NIHSS score upon admission	Continuous variable
Presence of underlying pulmonary disease	Categorical (no = 0, yes = 1)
Concurrent hypertension	Categorical (no = 0, yes = 1)
Mechanical ventilation	Categorical (no = 0, yes = 1)
Aspiration	Categorical (no = 0, yes = 1)
Confusion	Categorical (no = 0, yes = 1)
CRP	Continuous variable
WBC	Continuous variable
NEU	Continuous variable

NIHSS: National Institute of Health stroke scale; CRP: C-reactive protein; WBC: white blood cell count; NEU: neutrophil count.

infection following thrombolytic therapy. We analyzed the predictive value of CRP and NIHSS for the occurrence of pulmonary infection post-thrombolysis. The area under the ROC curve (AUC) for CRP was 0.895 (P<0.001, 95% CI 0.837-0.953), and for NIHSS, it was 0.809 (P<0.001, 95% CI 0.717-0.902). The sensitivity and specificity of CRP for predicting pulmonary infection were 88.57% and 75.00%, respectively. For NIHSS, the sensitivity was 87.14%, and the specificity was 70.00% (**Figure 3**).

Comparison of clinicopathologic characteristics in acute ischemic stroke patients with different prognoses following intravenous thrombolysis with alteplase

Treatment data from all patients were collected, and patients were categorized into a good prognosis group (75 cases) and a poor prognosis group (35 cases) based on their final recovery outcome. Analysis of clinicopathologic characteristics revealed that higher NIHSS scores at admission, elevated FIB levels, a thrombolysis time window greater than 3 hours, and the presence of pulmonary infection were associated with poor prognosis (P<0.05) by univariate analysis (**Table 5**). Further analysis using logistic regression identified high NIHSS scores at admission, elevated FIB levels, a thrombolysis time window greater than 3 hours, and the presence of pulmonary infection as independent risk factors for poor prognosis (**Tables 6**, **7**; **Figure 4**, P<0.05).

Predictive value of NIHSS scores and FIB levels for patient prognosis

We assessed the predictive value of NIHSS scores and FIB levels for patient prognosis. The area under the ROC curve (AUC) was 0.890 for NIHSS and 0.854 for FIB, both with P<0.001. The sensitivity and specificity of NIHSS for predicting poor prognosis were 89.33% and 82.86%, respectively, with a cutoff value of 14.50. For FIB, the sensitivity was 84.00%, and the specificity was 82.86%, with a cutoff value of 3.995. The combined detection of NIHSS score and FIB levels yielded an AUC of 0.922, with a sensitivity of 91.43% and a speci-

Table 4. Risk factors for pulmonary infection in stroke patients

Factor	B	S.E.	Wals	P	OR	95% C.I.	
						Lower limit	Upper limit
Age	0.201	0.231	8.971	0.013	3.145	1.076	8.993
Thrombolysis time window	0.012	0.367	1.223	0.119	1.011	0.521	2.423
NIHSS score upon admission	0.833	0.251	9.711	0.004	2.233	1.371	4.129
Presence of underlying pulmonary disease	1.591	0.731	10.201	0.001	4.559	1.928	9.322
Concurrent hypertension	0.724	0.686	1.113	0.021	2.062	0.537	7.912
Mechanical ventilation	1.600	0.671	5.668	0.017	1.955	1.330	18.459
Aspiration	3.332	0.871	14.619	0.321	1.996	5.073	14.491
Confusion	2.571	0.722	12.688	0.154	1.097	3.178	53.822
CRP	1.600	0.671	5.668	0.017	1.955	1.330	18.459
WBC	3.332	0.871	14.619	0.321	1.996	5.073	14.491
NEU	2.571	0.722	12.688	0.154	1.097	3.178	53.822

NIHSS: National Institute of Health stroke scale; CRP: C-reactive protein; WBC: white blood cell count; NEU: neutrophil count.

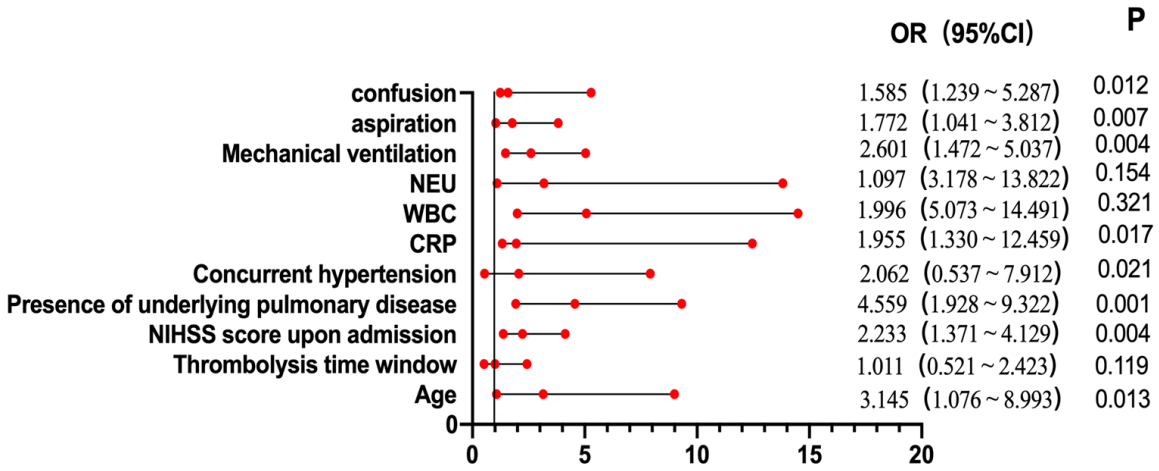

Figure 2. Risk factors for pulmonary infection in stroke patients. NEU: neutrophil count; CRP: C-reactive protein; WBC: white blood cell count.

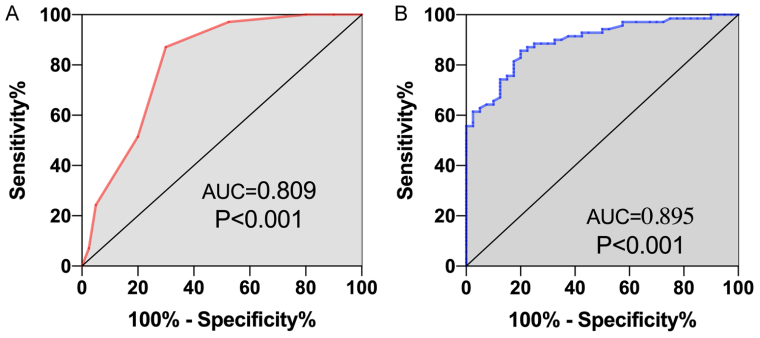

Figure 3. ROC Curves for NIHSS and CRP in predicting pulmonary infection after thrombolysis. A: ROC Curves for NIHSS in predicting pulmonary infection after thrombolysis; B: ROC Curves for CRP in predicting pulmonary infection after thrombolysis. NIHSS: National Institute of Health stroke scale; CRP: C-reactive protein.

ficity of 85.33%, indicating a high predictive value (**Figure 5**).

Discussion

Following an ischemic stroke, the immune system undergoes significant alterations, leading to prolonged immunosuppression and an increased risk of post-stroke infection. Severe cerebral ischemia triggers an immune activation response, which can exacerbate the neurological deficits caused by the

Table 5. Univariate analysis

Factor	Good prognosis group (n = 75)	Poor prognosis group (n = 35)	χ^2	P
Gender			0.140	0.709
Male (n = 60)	40 (53.33)	20 (57.14)		
Female (n = 50)	35 (46.67)	15 (42.86)		
Age			0.461	0.497
≥60 (n = 64)	42 (56.00)	22 (62.86)		
<60 (n = 46)	33 (44.00)	13 (37.14)		
Thrombolysis time window			7.082	0.008
≥3 h (n = 55)	31 (41.33)	24 (68.57)		
<3 h (n = 55)	44 (58.67)	11 (31.43)		
Combined lung infection			31.90	<0.001
Yes (n = 40)	14 (18.67)	26 (74.29)		
No (n = 70)	61 (81.33)	9 (25.71)		
NIHSS score upon admission	13.29±1.18	15.54±1.48	9.084	<0.001
WBC ($\times 10^9$/L)	8.59±0.3	8.61±0.3	0.356	0.745
NEU ($\times 10^9$/L)	6.85±0.28	6.76±0.31	1.517	0.132
LYM ($\times 10^9$/L)	2.12±0.23	2.09±0.23	0.850	0.397
CRP (mg/L)	6.34±0.69	6.41±0.63	0.509	0.621
D-D	1.27±0.31	1.29±0.32	0.312	0.756
FIB (g/L)	3.76±0.27	4.12±0.25	5.403	<0.001

NIHSS: National Institute of Health stroke scale; CRP: C-reactive protein; WBC: white blood cell count; LYM: lymphocyte count; D-D: D-dime; FIB: fibrinogen.

Table 6. Independent variables and their assigned values

Variable	Assigned Value
NIHSS score upon admission	≥3 h = 1, <3 h = 0
FIB (g/L)	Continuous variable
Thrombolysis time window	Continuous variable
Combined lung infection	Categorical (no = 0, yes = 1)

NIHSS: National Institute of Health Stroke Scale; FIB: fibrinogen.

stroke [13, 14]. Pulmonary infection has been identified as one of the most common complications post-stroke, significantly contributing to poor clinical outcomes and higher in-hospital mortality rates [15].

Our findings from both univariate and multivariate logistic regression analyses indicate that age, NIHSS score at admission, pre-existing pulmonary conditions, hypertension, and elevated CRP levels were independent risk factors for developing pulmonary infections after a stroke. It is well-established that stroke patients, often elderly, are more vulnerable to pulmonary infections due to increased frailty and compromised immune systems [16]. Higher NIHSS scores, reflecting more severe clinical presentations and greater impairment of consciousness and medullary function, are associated with a higher risk of pulmonary infection [17]. Therefore, it is crucial for healthcare providers to closely monitor these patients and actively engage in their rehabilitation to ensure a smooth transition from hospital to home.

Hypertension subjects blood vessels to sustained elevated pressure, damaging endothelial cells and contributing to atherosclerosis and thrombus formation. Chronic respiratory conditions and elevated NIHSS scores can lead to heart failure and impaired immune function, thereby reducing the body's ability to eliminate pathogens and significantly increasing the risk of pulmonary infections. These findings are consistent with related studies [18, 19]. CRP, an inflammatory biomarker, rises significantly in response to infections or tissue damage. Cerebral ischemia and hypoxia following a stroke can trigger an inflammatory cascade, elevating CRP and other inflammatory markers. This response can further activate the immune system, exacerbating infections and increasing the risk of pulmonary infection [20].

Table 7. Multifactorial analysis of factors affecting poor prognosis of patients

Factor	B	S.E.	Wals	P	OR	95% C.I.	
						Lower limit	Upper limit
NIHSS score upon admission	1.802	0.579	9.692	0.002	4.097	1.978	17.812
FIB (g/L)	1.423	0.582	6.772	0.011	3.162	1.337	12.542
Thrombolysis time window	1.351	0.522	5.619	0.013	3.155	1.280	11.359
Combined lung infection	1.603	0.602	7.201	0.005	2.939	1.562	13.291

NIHSS: National Institute of Health Stroke Scale; FIB: fibrinogen.

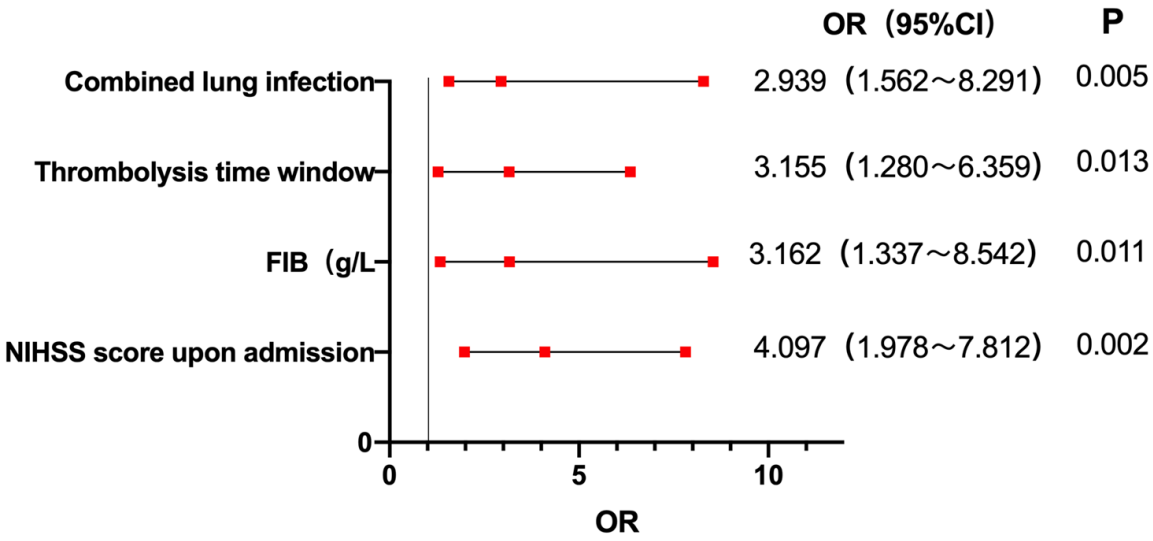

Figure 4. Risk factors for poor prognosis in patients. FIB: fibrinogen.

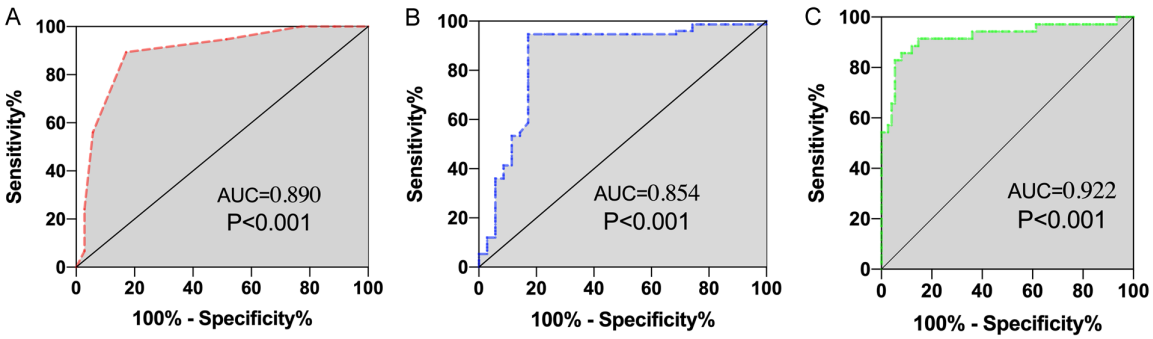

Figure 5. Analysis of the predictive value of NIHSS score and FIB for patient prognosis. A: ROC curve for NIHSS in predicting patient prognosis; B: ROC Curve for FIB in Predicting Patient Prognosis; C: Combined ROC curve for NIHSS Score and FIB in predicting patient prognosis. NIHSS: National Institute of Health stroke scale; CRP: C-reactive protein.

Our analysis also evaluated the predictive value of CRP levels and NIHSS scores for pulmonary infections in stroke patients post-thrombolysis. The AUC for CRP was 0.895 (P<0.001, 95% CI 0.837-0.953), and for NIHSS, it was 0.809 (P<0.001, 95% CI 0.717-0.902), indicating that both CRP and NIHSS scores are valuable predictors of pulmonary infections in stroke patients after thrombolysis. Our study identified high NIHSS scores upon admission, elevated FIB levels, a thrombolysis time window exceeding 3 hours, and the presence of concurrent pulmonary infections as independent risk factors for poor prognosis in stroke patients. The

NIHSS score at admission serves as an indicator of the initial degree of neurologic impairment and correlates with disease severity [21]. Previous research has shown that NIHSS scores at admission can affect early thrombolytic success [22].

Furthermore, the primary objective of thrombolysis is to rapidly reestablish blood flow to the ischemic penumbra within the infarcted region. A shorter duration from the onset of symptoms to the initiation of thrombolysis is generally associated with a smaller ischemic area and less severe hypoxic injury to brain tissue [23]. Alteplase, the thrombolytic agent, functions by activating plasminogen bound to fibrin within the thrombus, thereby dissolving fibrin, reducing FIB levels in the blood, and breaking down the thrombus. Intravenous thrombolysis can reduce FIB concentrations by up to 60% within 4 hours [24]. Therefore, patients with stroke-associated pneumonia or symptomatic hemorrhagic transformation following acute cerebral infarction require prompt and targeted symptomatic management to prevent further clinical deterioration.

It is important to note that FIB is a precursor to the fibrin component of thrombi and plays a significant role in the body's inflammatory response, contributing to acceleration of atherosclerosis, plaque formation, and thrombus development. Hyperfibrinogenemia has emerged as an independent risk factor for cerebrovascular disease, with elevated FIB levels post-thrombolysis in stroke patients indicating a poorer prognosis [25]. For patients presenting with acute cerebral infarction and high NIHSS scores at admission, aggressive and timely intervention is essential to mitigate the condition, prevent further neurological decline, and reduce the risk of pulmonary infection. Additionally, minimizing the time to treatment following admission can help prevent the expansion of the core infarct zone, thereby improving clinical outcomes.

However, there were several limitations. First, we did not conduct long-term follow-up, so the long-term prognostic impact of these factors remains unclear. Second, as a single-center study, our sample size was limited. Finally, since this was a retrospective analysis, the results may have inherent biases. Therefore, future research should include follow-up studies and larger sample sizes.

In conclusion, these findings indicate that factors such as age, NIHSS score, underlying lung disease, hypertension, and elevated CRP levels significantly contribute to the risk of pulmonary infection in acute ischemic stroke patients. Clinicians should closely monitor these data to manage the risk of pulmonary infection effectively.

Disclosure of conflict of interest

None.

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