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ORIGINAL RESEARCH

Correlation Between Serum D-Dimer, NLR, and CRP/ALB in Patients with Acute Ischemic Stroke

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Objective: This study examines the association between serum D-dimer (D-D), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein to albumin ratio (CRP/ALB), and the prognosis of intravenous thrombolysis in patients with acute ischemic stroke (AIS).

Methods: Ninety AIS patients admitted from June 2021 to October 2023 were included and divided into poor prognosis (29 cases) and good prognosis groups (61 cases) based on 90-day follow-up modified Rankin Scale (mRS) scores. Binary logistic regression identified prognostic factors, while ROC analysis evaluated the predictive efficacy of D-D, NLR, and CRP/ALB. Correlations among these markers were also analyzed.

Results: Binary logistic regression showed that age, D-D, ALB, CRP/ALB, neutrophil count, lymphocyte count, and NLR were significant prognostic risk factors ($P < 0.05$). ROC analysis yielded AUC values of 0.683 for D-D, 0.769 for NLR, and 0.728 for CRP/ALB, with combined AUC reaching 0.803. Sensitivity and specificity were 96.6%/39.3% for D-D, 100.0%/68.9% for NLR, and 100.0%/45.9% for CRP/ALB. Spearman correlation analysis revealed positive correlations among D-D, NLR, and CRP/ALB ($r = 0.367, 0.482, 0.462$, $p < 0.05$).

Conclusion: Age, D-D, ALB, CRP/ALB, neutrophil count, lymphocyte count, and NLR are significant prognostic factors for intravenous thrombolysis in AIS patients. D-D, NLR, and CRP/ALB are effective indicators for predicting prognosis, with combined prediction showing greater efficacy.

Keywords: acute ischemic stroke, D-dimer, intravenous thrombolysis, lymphocyte count, neutrophil count

Introduction

Acute ischemic stroke (AIS) is a prevalent neurological condition with a prognosis influenced by various factors. Recent research has highlighted the potential of serum biomarkers in prognostic assessments of AIS.[1] Serum D-dimer (D-D) levels, reflecting thrombosis extent in vivo, have been linked to AIS severity and poor outcomes.[2,3] This suggests a potential association between elevated D-D levels and unfavorable prognosis post-intravenous thrombolytic therapy. Neutrophil-to-lymphocyte ratio (NLR) serves as a straightforward inflammation indicator, revealing the body's inflammatory status and immunosuppression levels through neutrophil and lymphocyte proportions.[4] Studies suggest a high NLR may correlate with hemorrhagic transformation and poor AIS prognosis.[4] The CRP/ALB ratio, reflecting both inflammatory response and nutritional status, may also influence AIS prognosis, with a high ratio potentially indicating deterioration and poor outcomes. As D-D, NLR, and CRP/ALB as biomarkers based on their established associations with inflammation, coagulation, and overall disease severity in AIS patients, these biomarkers were chosen to provide a comprehensive assessment of the inflammatory and coagulation status in AIS patients, which are critical factors influencing the prognosis of intravenous thrombolysis.[5,6] Thus, the study aims to explore whether the combination of D-D, NLR, and CRP/ALB can enhance prognostic accuracy for intravenous thrombolysis in AIS patients compared to individual biomarkers, meanwhile to explore the relationship between serum D-D, NLR, CRP/ALB, and the prognosis of intravenous thrombolysis in patients with AIS.

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Data and Methods

General Data

In this study, 90 patients who were diagnosed with AIS and had been admitted to our hospital between June 2021 and October 2023 were enrolled. The inclusion criteria was: ① those who met the diagnostic criteria specified in the *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (2018)* and underwent intravenous thrombolysis treatment with rt-PA at our institution;[7] ② those aged between 18 and 90 years; and ③ those who had provided informed consent along with their families Exclusion criteria for this study were: ① those with severe insufficiency of vital organ function; ② those who could not tolerate the study method; ③ those with arteriovenous malformations, intracranial hemorrhage, multilobar infarction, or tumors; ④ individuals with cognitive disorders who could not cooperate with this study; ⑤ those with abnormal coagulation function; ⑥ those with venous system thrombosis; ⑦ Those with recent inflammatory diseases. The patients were divided into 29 cases in the poor prognosis group and 61 cases in the good prognosis group according to their mRS scores at the 90-day follow-up. The study protocol received approval from the institutional ethics committee.

Methods

After 90 days of treatment, patients' symptoms and living capacity limitations were assessed using the modified Rankin Scale (MRS).[8] This scale ranges from 0 (asymptomatic) to 5 (severely disabled, bedridden, requiring continuous care), with 6 indicating death. For this study, a poor prognosis was defined as death or an MRS score > 2, while an MRS score ≤ 2 indicated a good prognosis.

D-D levels were measured at various time points during the patient's hospitalization. Blood samples were collected upon admission, 24 hours after the initiation of thrombolytic therapy, 7 days post-treatment initiation, and at discharge. The samples were collected using disposable anticoagulant tubes (sodium citrate in a 1:9 ratio). D-D levels were assessed using the CN-6000 reagent kit from Sysmex Corporation, employing the latex agglutination method, and analyzed with a fully automated coagulation analyzer (SYSMEXCA-7000).

CRP and ALB levels were measured using the Roche cobas c 702, a fully automated biochemistry instrument. The C-reactive protein albumin ratio (CAR) was then calculated. Neutrophil (NE) and lymphocyte (LY) levels were assessed using the Myriad BC-6900, a fully automated hematology analyzer from Mindray Bio-Medical Electronics Co., Ltd. NLR were subsequently calculated. All tests were conducted strictly following the operating procedures and reagent instructions of the respective instruments.

Observation Indexes

The research investigated the factors affecting the prognosis of intravenous thrombolysis in patients with AIS through binary logistic regression. It assessed the predictive ability of serum D-D, NLR, and CRP/ALB for the prognosis of intravenous thrombolysis using ROC analysis. Moreover, the study explored the relationship between serum D-D, NLR, and CRP/ALB.

Statistical Processing

Data analysis was conducted using SPSS 22.0. Count data were presented as (n, %) and analyzed using the χ^2 test. Normally distributed measurement data were expressed as ($\bar{x} \pm s$) and compared between groups using independent samples *t*-test. For data that did not follow a normal distribution, the quartile median was used. Nonparametric tests were performed, and binary logistic regression was utilized to identify influencing factors. The diagnostic value was evaluated using ROC curve analysis, and Spearman correlation coefficient was employed for correlation analysis. A significance level of $P < 0.05$ was used to indicate statistical significance.

Results

Univariate Analysis of the Two Groups

Univariate analysis showed no statistically significant difference between the two groups regarding gender ($P > 0.05$). However, there were significant differences between the two groups in terms of age, D-D, CRP, ALB, CRP/ALB ratio, neutrophil count, lymphocyte count, NLR, and admission mRS score ($P < 0.05$, Table 1).

Logistic Regression Analysis of Prognostic Influencing Factors

A binary regression analysis was performed with "prognostic status" as the dependent variable (coded as 0 for good prognosis and 1 for bad prognosis) and "age, D-D, CRP, ALB, CRP/ALB, neutrophil count, lymphocyte count, NLR, admission mRS score" as the independent variables. The analysis demonstrated that age, D-D, ALB, CRP/ALB, neutrophil count, lymphocyte count, and NLR were significant prognostic risk factors ($P < 0.05$, Tables 2 and 3).

Table 1 Univariate Analysis of the Two Groups

Indicator	Classification	Good Prognosis Group (61)	Poor Prognosis Group (29)	t/χ^2 value	*P* value
Sex	Male	39(63.93)	13(44.83)	2.941	0.086
	Female	22(36.07)	16(55.17)		
Age (years)		64.85±12.62	74.34±9.31	3.606	0.001
D-D (ug/mL)		0.40(0.29, 0.89)	0.57(0.41, 1.61)	2.803	0.005
CRP (mg/L)		3.78(1.53, 16.17)	15.19(12.20, 19.25)	4.170	<0.001
ALB (g/L)		40.99±3.88	38.72±4.73	2.408	0.018
CRP/ALB		0.09(0.04, 0.39)	0.37(0.32, 0.56)	4.113	<0.001
Neutrophil count (10^9/L)		5.05(4.00, 6.43)	6.18(5.60, 6.51)	3.009	0.002
Lymphocyte count (10^9/L)		1.55(1.15, 2.03)	1.31(0.96, 1.54)	2.577	0.005
NLR		3.20(2.15, 5.00)	4.66(3.76, 6.52)	3.475	<0.001
Admission mRS score (points)		0.07±0.25	0.34±0.86	2.357	0.021

Table 2 Logistic Regression Assignment of Prognostic Influences

Variable	Variable Name	Assignment Method
Prognostic status	Y	Good prognosis = 0, poor prognosis = 1
Age (years)	X_1	Continuous variable
D-D	X_2	Continuous variable
CRP	X_3	Continuous variable
ALB	X_4	Continuous variable
CRP/ALB	X_5	Continuous variable
Neutrophil count (10^9/L)	X_6	Continuous variable
Lymphocyte count (10^9/L)	X_7	Continuous variable
NLR	X_8	Continuous variable
Admission mRS score (points)	X_9	Continuous variable

Table 3 Logistic Regression Analysis of Prognostic Influences

	B	S.E.	Wald	df	*P*	OR	95% C.I	
							Lower Limit	Upper Limit
Age (years)	0.081	0.025	10.18	1	0.001	1.084	1.032	1.140
DD	0.645	0.300	4.612	1	0.032	1.905	1.058	3.431
CRP	0.023	0.013	3.141	1	0.076	1.023	0.998	1.049

(*Continued*)

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Table 3 (Continued).

	B	S.E.	Wald	df	*P*	OR	95% C.I	
							Lower Limit	Upper Limit
ALB	−0.129	0.056	5.246	1	0.022	0.879	0.787	0.982
CRP/ALB	0.972	0.527	3.401	1	0.045	2.644	0.941	7.429
Neutrophil count (10^9/L)	0.275	0.126	4.746	1	0.029	1.316	1.028	1.685
Lymphocyte count (10^9/L)	−1.336	0.518	6.659	1	0.010	0.263	0.095	0.725
NLR	0.243	0.099	6.062	1	0.014	1.275	1.051	1.547
Admission mRS score (points)	1.167	0.614	3.618	1	0.057	3.213	0.965	10.697
Constant	−0.924	0.246	14.097	1	<0.001	0.397		

Table 4 Efficacy of Serum D-D, NLR, CRP/ALB, and Combined Data in Predicting Prognosis of Intravenous Thrombolysis in Patients with AIS

Indicator	AUC	Standard Error	*P*	95% CI		Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index
				Lower Limit	Upper Limit				
D-D	0.683	0.058	0.005	0.570	0.797	0.325	96.6	39.3	0.359
Ratio	0.769	0.049	<0.001	0.672	0.866	0.255	100.0	68.9	0.689
NLR	0.728	0.052	0.001	0.626	0.829	2.910	100.0	45.9	0.459
Combination of three items	0.803	0.048	<0.001	0.679	0.867	2.0685	100.0	70.8	0.708

Notes: Combination of three item: combine of D-D, Ratio, NLR.

Efficacy of Serum D-D, NLR, CRP/ALB, and Combined Data in Predicting the Prognosis of Intravenous Thrombolysis in Patients with AIS

The areas under the curve (AUCs) for serum D-D, NLR, and CRP/ALB in predicting the prognosis of intravenous thrombolysis in patients with AIS, as determined by ROC analysis, were 0.683, 0.769, and 0.728, respectively. These values corresponded to sensitivities and specificities of 96.6%/39.3%, 100.0%/68.9%, and 100.0%/45.9%, respectively.

D-D, NLR, and CRP/ALB were integrated into the logistic regression model. The formula for calculating the composite score derived from the regression coefficients was: three-item combined score = D-D + (0.972/0.645) * CRP/ALB + (0.243/0.645) * NLR. Statistical analysis yielded data for the three-item composite score, with the combined prediction AUC for patients with AIS undergoing intravenous thrombolysis being 0.803, with a sensitivity of 100.0% and a specificity of 70.8% (Table 4 and Figure 1).

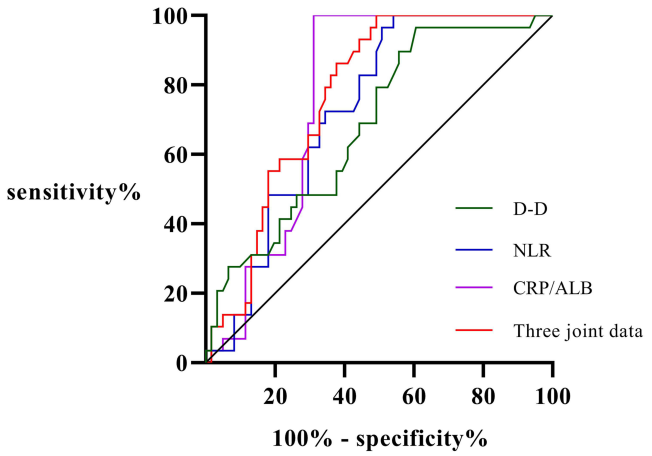

Figure 1 ROC curves of D-D, NLR, CRP/ALB, and combined data in predicting the prognosis of intravenous thrombolysis in AIS.

Table 5 Correlation Analysis of Serum D-D, NLR, CRP/ALB

Spearman Rank Correlation		DD	CRP/ALB	NLR
DD	Correlation coefficient (r-value)	-	0.367	0.482
	P-value (two-tailed)	-	<0.001	<0.001
CRP/ALB	Correlation coefficient (r-value)	0.367	-	0.462
	P-value (two-tailed)	<0.001	-	-
NLR	Correlation coefficient (r-value)	0.482	0.462	-
	P-value (two-tailed)	<0.001	<0.001	
N		90	90	90

Analysis of the Correlation Between Serum D-D, NLR, and CRP/ALB

Spearman rank correlation analysis revealed a positive correlation among D-D, NLR, and CRP/ALB ($r = 0.367, 0.482, 0.462$, $p < 0.05$, Table 5).

Discussion

AIS, also referred to as cerebral infarction, manifests as impaired brain function due to a temporary or permanent interruption of blood flow to the brain. It constitutes the most prevalent form of cerebrovascular disease, representing about 80% of all stroke cases.[9–11] AIS poses a substantial global public health challenge. Timely diagnosis and prognosis assessment are paramount for managing patients with AIS. Early diagnosis facilitates the prompt initiation of therapeutic interventions like intravenous thrombolysis and mechanical thrombolysis, aimed at restoring cerebral blood flow and minimizing brain injury.[12] Moreover, early prognosis assessment allows physicians to gauge the severity of the patient's condition, monitor physiological indicators, and anticipate potential complications, which guides appropriate treatment decisions. Serum D-D, a blood biochemical marker serves to evaluate coagulation system activity. It is significant in blood coagulation and fibrinolysis processes and aids as an additional diagnostic indicator for AIS.[3] NLR, representing the neutrophil-to-lymphocyte ratio offers insight into inflammation and immune status by assessing the ratio of neutrophil count to lymphocyte count.[13] CRP, short for C-reactive protein, is synthesized by the liver, with its levels notably elevated during acute inflammatory responses.[14]

In this study, 90 patients with AIS were prospectively enrolled from our hospital between June 2021 and October 2023. These patients were categorized into two groups based on their 90-day follow-up mRS scores: 29 cases in the poor prognosis group and 61 cases in the good prognosis group. The CRP/ALB ratio was inflammatory ratios due to its unique integration of acute inflammatory response and overall nutritional status. This combination provides a more comprehensive reflection of the patient's systemic condition, which is crucial for predicting outcomes in AIS. Unlike single markers or other ratios, CRP/ALB can capture both the inflammatory burden and the patient's resilience, making it a more informative prognostic indicator. The findings highlighted age, D-D, ALB, CRP/ALB, neutrophil count, lymphocyte count, and NLR as prognostic risk factors ($P < 0.05$). Age emerged as a notable risk factor due to age-related declines in recovery capacity and metabolic function, rendering patients more vulnerable to ischemic stroke and potentially leading to a poorer prognosis. Elevated levels of D-dimer (D-D), a coagulation indicator, may signify aberrant activation of the blood coagulation and fibrinolytic systems. In AIS, heightened D-D levels could indicate intravascular thrombosis presence, which is associated with an unfavorable prognosis.[3] Albumin levels serve as vital indicators of the body's nutritional status, with low levels potentially indicating malnutrition or an elevated inflammatory state.[15] Reduced albumin levels are associated with unfavorable outcomes, including delayed functional recovery and heightened complication risks. The C-reactive protein (CRP) to albumin (ALB) ratio serves as an indicator of both inflammation severity and nutritional status. A high CRP/ALB ratio often suggests a pronounced inflammatory response and malnutrition, both of which are correlated with poor prognosis in patients with ischemic stroke.

Neutrophils and lymphocytes play pivotal roles in the immune system. In AIS, an increase in neutrophil counts alongside a decrease in lymphocyte counts may signify disruptions in the body's inflammatory response and immune function. This imbalance in immune-inflammatory dynamics could contribute to neurological impairment and exacerbate

prognosis. The NLR which reflects the ratio between neutrophil and lymphocyte counts is commonly elevated during inflammatory states and immune dysfunction. Elevated NLR levels are associated with increased severity and poorer prognosis in cases of cerebral infarction.[16–18] The AUCs of serum D-D, NLR, and CRP/ALB analyzed by ROC to predict the prognosis of intravenous thrombolysis in patients with AIS were 0.683, 0.769, and 0.728, respectively. When combined, the AUC for all three indicators reached 0.803, with a sensitivity of 100.0% and a specificity of 70.8%. Combining multiple indicators offers a more comprehensive assessment of the patient's condition and prognostic risk, as each metric reflects different biological processes and mechanisms.

This combined approach enhances the accuracy of predictions by considering a broader range of factors. The prognosis of AIS depends on various factors such as vascular, inflammatory, and immune statuses. While a single indicator may capture only certain aspects of these factors, combining multiple indicators offers a more holistic assessment, thus improving prediction accuracy. Each indicator contributes unique information: D-D reflects intravascular thrombosis, NLR indicates inflammatory and immune status, and the CRP/ALB ratio reflects inflammation and nutritional status. By integrating these indicators, a more accurate prognosis of a patient's condition can be obtained, which focuses on thrombosis, inflammation, and nutrition collectively. Utilizing multiple indicators together enhances predictive accuracy, as a single indicator may not adequately capture the complexity of AIS prognosis and could lead to misclassification or incomplete predictions. However, when multiple indicators are combined, they can complement each other and increase the accuracy and reliability of predictions.

Spearman rank correlation analysis revealed a positive correlation between D-D, NLR, and CRP/ALB ($r = 0.367$, 0.482, 0.462, $p < 0.05$). AIS triggers an inflammatory response, leading to elevated levels of inflammatory markers like D-D, NLR, and CRP. This response is pivotal in ischemic stroke, as it releases inflammatory mediators and cytokines, promoting the aggregation of inflammatory cells and amplifying the overall response. Consequently, the positive correlation among D-D, NLR, and CRP/ALB may underscore their shared involvement in the inflammatory process. While D-D serves as an indicator of intravascular thrombolytic products, reflecting the process of thrombus formation and lysis, NLR and CRP/ALB are closely linked to inflammation and immune function. In ischemic stroke, these biological processes likely interact, resulting in the observed positive correlation among D-D, NLR, and CRP/ALB. The onset and progression of AIS involve various pathological mechanisms, including the inflammatory response, activation of the coagulation system, and immune cell activation. These mechanisms are interconnected and mutually influence one another, with D-D, NLR, and CRP/ALB potentially reflecting these complex interactions. Multiple studies have shown that a higher baseline NIHSS score, hyperglycemia at admission, and intracerebral hemorrhage following alteplase treatment are independent predictors of poor outcomes at three months (mRS > 2).[19–21] Meanwhile, other studies focusing on different subtypes of hemorrhagic infarction after alteplase treatment have found that a higher baseline NIHSS score, cardioembolic stroke, and atrial fibrillation are independent predictors of all subtypes of hemorrhagic infarction. Anterior circulation stroke is an independent predictor of hemorrhagic infarction type 1 and 2, while older age is also an independent predictor of parenchymal hematoma type 1.[22–24] This study provides valuable insights into the prognostic value of D-D, NLR, and CRP/ALB in AIS patients undergoing thrombolysis and provide candidate biomarkers. However, it has several limitations that warrant further exploration. Future research should investigate why CRP/ALB outperforms individual CRP or ALB measurements, potentially due to its integration of both inflammatory and nutritional statuses. Additionally, the direct mechanisms by which elevated NLR contributes to poor prognosis, such as neutrophil extracellular traps or lymphocyte exhaustion, require more detailed examination. The study also lacks cutoff values for clinical decision-making, which are essential for practical application of the combined score.[25,26] Potential confounders, including thrombolytic drug dosage and time-to-treatment, should be addressed in future analyses. Given the retrospective design and potential biases in patient selection, validation in larger, multi-center cohorts is recommended. Future studies could also explore incorporating additional biomarkers to enhance prognostic accuracy.

Conclusion

In conclusion, our study identifies age, D-D, ALB, CRP/ALB, neutrophil count, lymphocyte count, and NLR as significant prognostic factors for intravenous thrombolysis in patients with AIS. The combined use of D-D, NLR, and CRP/ALB demonstrates enhanced predictive accuracy. While the preliminary results suggest promising sensitivity and

specificity, further validation is necessary to confirm the robustness and generalizability of these findings. Future research should focus on validating these results in larger, multicenter cohorts to address potential biases and ensure the reliability of the combined scoring system. Additionally, exploring the incorporation of other biomarkers and clinical parameters may further improve prognostic accuracy.

Abbreviations

AIS, acute ischemic stroke; D-D, D-dimer; NLR, Neutrophil lymphocyte ratio; CRP, C-reactive protein; ALB, albumin; CAR, C-reactive protein albumin ratio; ROC, receiver operating characteristic; AUC area under roc curve.

Data Sharing Statement

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of The People's Hospital of the Qiandongnan Miao and Dong Autonomous Prefecture. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest regarding this work.

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