Relationship between Advanced Lung Cancer Inflammation Index and 3-month Outcome in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis

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Abstract

Objectives: The Advanced Lung Cancer Inflammatory index (ALI) has been established as a reliable prognostic marker for cardiovascular and cerebrovascular diseases. However, the relationship between ALI and outcome in acute ischemic stroke (AIS) patients treated with intravenous thrombolysis (IVT) remains unclear.

Methods: This study enrolled 784 AIS patients treated with IVT all of whom were followed up for at least 3 months after treatment. 3-month post-thrombolysis non-excellent outcome was defined as the modified Rankin Scale ranging from 2 to 6. The research investigated the relationship between ALI and non-excellent outcome in AIS patients treated with IVT, via multivariate logistic models and restricted cubic spline (RCS) analyses, etc.

Results: When the patients were divided into four quartiles (Q) based on ALI levels, we found that those with lower ALI levels were more likely to experience non-excellent outcome ($P < 0.001$). The multivariate logistic model revealed that reduced ALI levels (odds ratio [OR]: 0.487, 95% confidence interval [CI]: 0.310–0.767, $P = 0.002$) were significant associated with non-excellent outcomes (ALI Q4 *vs*. Q1) after the adjustment of confounding factors. RCS analyses exhibited a non-linear J-shaped pattern ($P_{overall} = 0.003$, $P_{nonlinear} = 0.013$).

Conclusion: Decreased levels of ALI might be associated with post-thrombolysis non-excellent outcome in AIS patients.

Keywords: advanced lung cancer inflammation index; biomarker; functional outcome; acute ischemic stroke; intravenous thrombolysis

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Worldwide, stroke remains a critical public health challenge, imposing a substantial burden on healthcare systems and individuals[1]. Acute ischemic stroke (AIS) is responsible for most stroke cases[1]. At present, intravenous thrombolysis (IVT) is regarded as an effective treatment for AIS patients[2–4]. Nevertheless, despite receiving IVT treatment, numerous AIS patients might still experience non-excellent functional outcomes. As a result, it is crucial to identify reliable and accessible biomarkers for functional outcomes in AIS patients treated with IVT.

The Advanced Lung Cancer Inflammatory Index (ALI), a novel biomarker, was initially reported to correlate with poor prognosis in patients with advanced non-small cell lung cancer (NSCLC)[5]. Studies have demonstrated that lower ALI values serve as a reliable prognostic indicator for overall survival in various diseases. Specifically, ALI reflects systemic inflammation through three biomarkers: body mass index (BMI), serum albumin (ALB), and the neutrophil-to-lymphocyte ratio (NLR), thereby predicting patient survival[6]. Notably, ALI revealed prognostic value not only in lung cancer but also in other diseases such as cholangiocarcinoma and specific cardiovascular disorders. Studies indicated that low levels of ALI correlated with higher mortality risks in these patients[7–11]. As a readily available biomarker, ALI may hold significant clinical potential to assist clinicians in better assessing patient prognosis and developing personalized treatment plans[12,13].

Because the relationship between ALI and outcome in AIS patients treated with intravenous thrombolysis remained unclear, coupled with the existing demand for prognostic tools in stroke management, we undertook the comprehensive analyses utilizing data from three stroke centers. The objective of this study was to examine the potential association between ALI and functional outcome in AIS patients treated with IVT.

Materials and methods

Study design and participants

The study flowchart and the inclusion as well as exclusion criteria are shown in Figure 1. AIS patients undergoing IVT within 4.5 h were recruited from the Nanjing First Hospital, Nantong Third People's Hospital and Affiliated Hospital of Nantong University. All the patients were treated in the stroke units. Eligible participants were enrolled in the final analysis if they met the following criteria. Informed consent was obtained from participants or their legal representatives. The study was approved by the Ethics Committee of Affiliated Hospital of Nantong University (2022-K145-01), Nantong Third People's Hospital, Affiliated Nantong Hospital 3 of Nantong University (EK2021026), and Nanjing First Hospital, Nanjing Medical University (2019-695).

Inclusion criteria: (1) Admission within 4.5 h after onset; (2) Treated with IVT; (3) 18 years or older. Exclusion criteria: (1) Severe inflammatory diseases or infectious

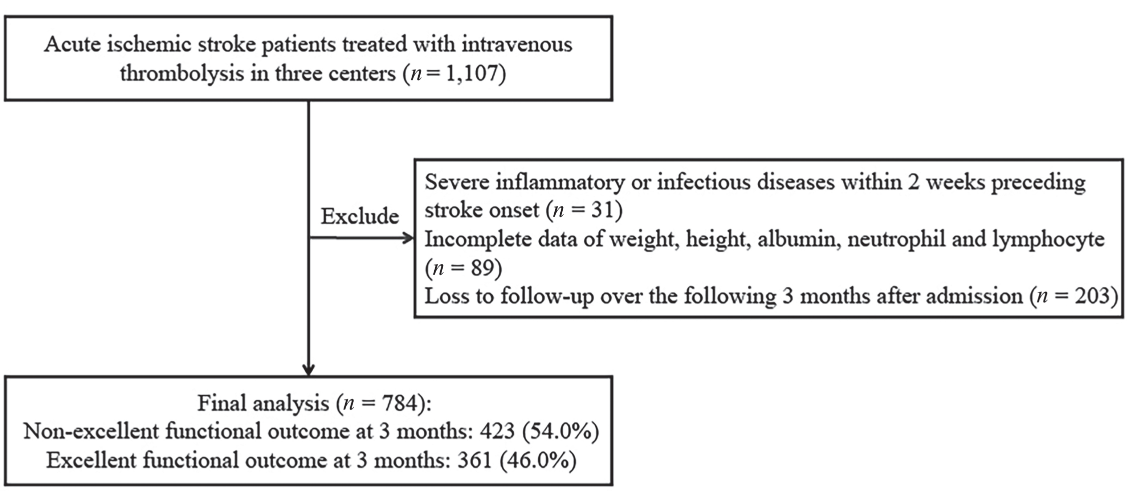

Figure 1: The flowchart of participants selection.

diseases within two weeks preceding stroke onset; (2) Incomplete data of weight, height, albumin, neutrophil and lymphocyte; (3) Loss to follow-up over the following 3 months after admission.

Data acquisition

On the day of admission, all the participants underwent standard assessments of demographic characteristics (age and gender), vascular risk factors (history of hypertension, history of diabetes mellitus, history of atrial fibrillation, history of coronary artery disease, current smoking, and current drinking alcohol), medication use (antiplatelet, anticoagulation), clinical assessment (stroke severity, onset to treatment time [OTT], proximal arterial occlusion [PAO], and stroke subtype). Computed tomography, magnetic resonance, electrocardiogram, echocardiography, carotid ultrasonography, and transcranial Doppler were performed for assessing stroke subtype and PAO. Stroke severity was assessed using National Institutes of Health Stroke Scale (NIHSS) score. Stroke subtype was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[14].

Calculation of ALI

ALI was calculated as body mass index (BMI) × albumin/neutrophil-to-lymphocyte ratio (NLR)[5–13]. BMI is calculated as the weight (kg)/height (m)^2. The ALI, serving as the exposure variable, was examined both as a continuous variable and following its categorization into four quartiles (Q).

Definition of 3-month non-excellent functional outcome

Modified Rankin Scale (mRS), ranging from 0 to 6, is a standard scale to assess the independent status, where higher scores denote poorer independence. To assess functional outcomes in the stroke patients, mRS is widely utilized. At the 3-month follow-up, standardized assessments were performed by certified neurologists via either structured telephone interviews or in-person clinic visits. The primary study outcome was non-excellent functional outcome, which was defined as mRS score ranging from 2 to 6. Meanwhile, excellent functional outcome was defined as mRS score ranging from 0 to 1[15–21].

Statistic analysis

Statistical analyses were performed using R version 4.5.1 software. All participants were categorized into 4 groups according to the Q of ALI. Categorical variables were expressed as *n* (%), and continuous variables were expressed as means (standard deviation, SD) or medians (interquartile range, IQR). Differences in baseline characteristics between groups were analyzed using one-way ANOVA or Mann-Whitney U test for continuous variables as well as the chi-squared test or Fisher's exact test for categorical variables, as appropriate. We used the violin plots to show the distribution of ALI between the excellent outcome group and non-excellent outcome group. Logistic regression models were performed to estimate associations between the levels of ALI and non-excellent functional outcome in AIS patients undergoing IVT. Model 1 was crude model. Model 2 was adjusted for age, gender, smoke and alcohol. Model 3 was adjusted for age, gender, smoke and alcohol, hypertension, diabetes, atrial fibrillation, coronary heart disease, PAO, TOAST group, OTT, antiplatelet therapy, anticoagulation therapy, triglyceride and low-density lipoprotein cholesterol (LDL-C). We further evaluated the trends and strength of the association between the levels of ALI and non-excellent functional outcome in AIS patients undergoing IVT using the restricted cubic splines (RCS) with 4 knots (at the 5th, 35th, 65th, and 95th percentiles) adjusted for model 3. Receiver operating characteristic (ROC) curve was used to test the overall discriminative ability of ALI for non-excellent functional outcome in AIS patients undergoing IVT.

Results

Baseline characteristics of AIS patients treated with IVT

We enrolled 784 AIS patients treated with IVT in Affiliated Hospital of Nantong University, Nanjing First Hospital, and Nantong Third People's Hospital. Table 1 presented the participant characteristics stratified by ALI quartiles. Lower ALI levels were more likely to experience non-excellent outcome ($P < 0.001$). Figure 2(a) illustrated the levels of ALI levels significantly in the excellent functional outcome group and the non-excellent functional outcome group. Figure 2(b) showed that the distribution of 90-day mRS scores significantly

Table 1: Characteristics of participants based on the Q of ALI

Characteristic	ALI				P
	Q1 (n = 196)	Q2 (n = 196)	Q3 (n = 196)	Q4 (n = 196)	
Age (%)					0.005
⩾ 65	143 (72.96)	155 (79.08)	130 (66.33)	126 (64.29)	
< 65	53 (27.04)	41 (20.92)	66 (33.67)	70 (35.71)	
Gender (%)					0.007
Female	63 (32.14)	85 (43.37)	63 (32.14)	88 (44.90)	
Male	133 (67.86)	111 (56.63)	133 (67.86)	108 (55.10)	
Vascular risk factors (%)					
Current drinking alcohol	64 (32.65)	69 (35.20)	67 (34.18)	55 (28.06)	0.441
Current smoking	66 (33.67)	69 (35.20)	78 (39.80)	57 (29.08)	0.166
History of diabetes mellitus	42 (21.43)	49 (25.00)	44 (22.45)	38 (19.39)	0.607
History of hypertension	135 (68.88)	136 (69.39)	136 (69.39)	119 (60.71)	0.194
History of atrial fibrillation	54 (27.55)	50 (25.51)	48 (24.49)	46 (23.47)	0.821
History of coronary heart disease	15 (7.65)	20 (10.20)	19 (9.69)	12 (6.12)	0.434
Clinical assessment (%)					
PAO	111 (56.63)	92 (46.94)	72 (36.73)	72 (36.73)	< 0.001
NIHSS group					0.002
Mild (0–4)	50 (25.51)	72 (36.73)	86 (43.88)	75 (38.27)	
Moderate (5–10)	70 (35.71)	72 (36.73)	65 (33.16)	67 (34.18)	
Moderately Severe (11–20)	56 (28.57)	45 (22.96)	38 (19.39)	47 (23.98)	
Severe (⩾ 21)	20 (10.20)	7 (3.57)	7 (3.57)	7 (3.57)	
Stroke subtype (TOAST)					0.459
LAA	99 (50.51)	99 (50.51)	96 (48.98)	96 (48.98)	
CE	20 (10.20)	31 (15.82)	29 (14.80)	34 (17.35)	
SAO	69 (35.20)	57 (29.08)	56 (28.57)	55 (28.06)	
Other/Unknown	8 (4.08)	9 (4.59)	15 (7.65)	11 (5.61)	
OTT					< 0.001
< 3 h	105 (53.57)	131 (66.84)	133 (67.86)	163 (83.16)	
3–4.5 h	91 (46.43)	65 (33.16)	63 (32.14)	33 (16.84)	
Medication use (%)					
Antiplatelet therapy					0.012
Never use	46 (23.47)	34 (17.35)	20 (10.20)	25 (12.76)	
New initiation post-stroke	132 (67.35)	142 (72.45)	160 (81.63)	149 (76.02)	
Use prior to stroke	18 (9.18)	20 (10.20)	16 (8.16)	22 (11.22)	
Anticoagulation therapy					0.639
Never Use	118 (60.20)	128 (65.31)	133 (67.86)	131 (66.84)	

(*continued*)

Table 1

(continued)

Characteristic	ALI				*P*
	Q1 (*n* = 196)	Q2 (*n* = 196)	Q3 (*n* = 196)	Q4 (*n* = 196)	
New initiation post-stroke	67 (34.18)	59 (30.10)	51 (26.02)	57 (29.08)	
Use prior to stroke	11 (5.61)	9 (4.59)	12 (6.12)	8 (4.08)	
Functional outcome (%)					< 0.001
Excellent	63 (32.14)	91 (46.43)	102 (52.04)	105 (53.57)	
Non-excellent	133 (67.86)	105 (53.57)	94 (47.96)	91 (46.43)	
LDL-C (mean [SD])	111.91 (33.95)	115.67 (31.34)	113.74 (33.02)	116.87 (30.40)	0.440
TG (mean [SD])	116.64 (76.93)	124.69 (67.70)	149.30 (115.97)	138.65 (81.56)	0.001

Note: ALI: Advanced Lung Cancer Inflammation Index; NIHSS: National Institutes of Health Stroke Scale; OTT: onset to treatment time; PAO: proximal arterial occlusion; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA: large-artery atherosclerosis; CE: cardioembolism; SAO: small-artery occlusion; SUE: stroke of undetermined etiology; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride.

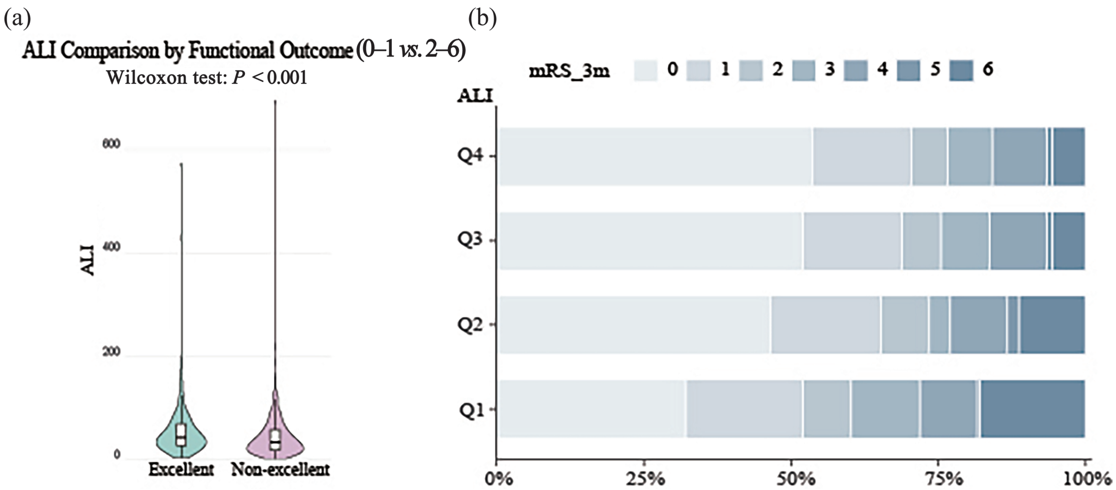

Figure 2: **Association between ALI levels and post-thrombolysis functional outcome ((a) Comparison of ALI levels between patients with excellent and non-excellent functional outcome; (b) Distribution of 90-day mRS scores across ALI Q groups).**

different in ALI quartile groups.

Relationship between ALI and 3-month non-excellent post-thrombolysis functional outcome

A total of 784 patients treated with IVT were recorded. The associations of ALI with 3-month non-excellent post-thrombolysis functional outcome is presented in Table 2. We employed the multivariate logistic regression model to estimate the independent associations of ALI with non-excellent post-thrombolysis functional outcome. In model 1, the OR and 95% CI from the lowest to the highest ALI Q (Q1–Q4) were 1.000 (reference), 0.547 (0.363–0.824), 0.437 (0.290–0.658), and 0.411 (0.272–0.619), respectively. In model 2, the OR and 95% CI from the lowest to the highest ALI Q groups (Q1–Q4) were 1.000 (reference), 0.502 (0.330–0.762), 0.440 (0.291–0.666), and 0.416 (0.274–0.631), respectively. After the adjustment for multiple variables (model 3), the OR and 95% CI for the lowest to the highest ALI quartiles (Q1–Q4) were 1.000 (reference), 0.530 (0.341–0.824), 0.527 (0.338–0.822), and 0.487 (0.310–0.767), respectively. Powerful evidence for a monotonically increasing dose-response relationship between decreased ALI levels and non-excellent post-thrombolysis functional outcome

Table 2: OR (95% CI) of ALI and post-stroke functional outcome in different models

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
ALI (continuous)	0.994 (0.990–0.998)	0.004	0.995 (0.991–0.999)	0.007	0.996 (0.992–0.999)	0.023
ALI (Q groups)						
Q1	Ref		Ref		Ref	
Q2	0.547 (0.363–0.824)	0.004	0.502 (0.330–0.762)	0.001	0.530 (0.341–0.824)	0.005
Q3	0.437 (0.290–0.658)	< 0.001	0.440 (0.291–0.666)	< 0.001	0.527 (0.338–0.822)	0.005
Q4	0.411 (0.272–0.619)	< 0.001	0.416 (0.274–0.631)	< 0.001	0.487 (0.310–0.767)	0.002
P for trend	< 0.001		< 0.001		0.004	

Note: Model 1 was adjusted for nothing; Model 2 was adjusted for age, gender, smoke and alcohol; Model 3 was adjusted for age, gender, smoke and alcohol, hypertension, diabetes, atrial fibrillation, coronary heart disease, large vessel occlusion, TOAST group, time from onset to admission, antiplatelet therapy, anticoagulation therapy, triglyceride and LDL-C. OR: odds ratio; CI: confidence interval; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LDL-C: low-density lipoprotein cholesterol; ALI: Advanced Lung cancer Inflammation Index.

was found across all statistical models: $P < 0.001$ in crude model, $P < 0.001$ in model 1, $P < 0.001$ in model 2, and $P = 0.004$ in the fully adjusted model 3.

RCS analysis investigating the relationship of ALI with 3-month non-excellent post-thrombolysis functional outcome

Figure 3 presented RCS analysis examining the relationship between ALI and non-excellent post-thrombolysis functional outcome. After adjustment by model 3, ALI showed a statistically significant negative correlation with 3-month non-excellent outcome, with the curve exhibiting a non-linear J-shaped pattern ($P_{overall} = 0.003$, $P_{nonlinear} = 0.013$). Specifically, when ALI is in the lowest Q group (Q1), the risk of poor prognosis is highest. Once ALI exceeds the 25th percentile (entering Q2, Q3, or Q4), the risk of poor prognosis decreases significantly. Notably, within the Q2–Q4 range, a platform effect exists, meaning further increases in ALI levels won't significantly reduce additional risks. To validate this platform effect, we reanalyzed multivariate logistic regression adjusted for model 3 with additional group comparisons (Table 3). Importantly, pairwise comparisons among the higher ALI groups (Q2–Q4) revealed no statistically significant differences in risk (Q3 *vs*. Q2, OR = 0.994, $P = 0.798$; Q4 *vs*. Q2, OR = 0.920, $P = 0.702$; Q4 *vs*. Q3, OR = 0.925, $P = 0.722$), suggesting a threshold effect where the primary risk occurs below the 25th percentile (22.79) of ALI.

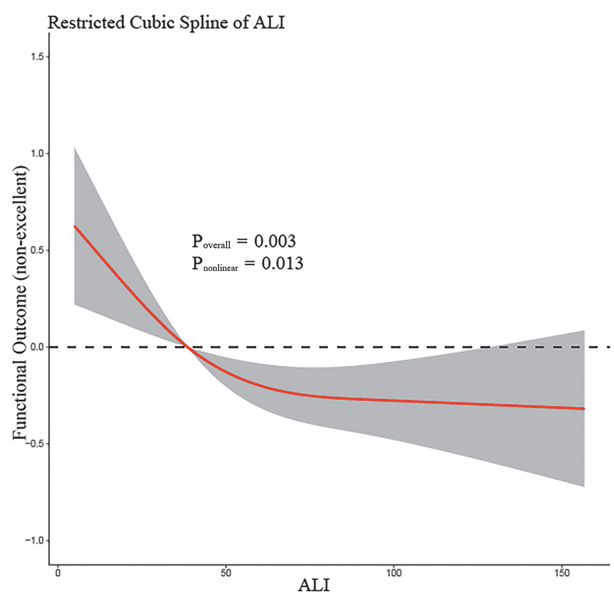

Figure 3: Restricted cubic spline analysis of ALI and non-excellent post-thrombolysis functional outcome.

Predictive values of ALI for non-excellent post-thrombolysis functional outcome

Figure 4 showed the predictive values of ALI for non-excellent post-thrombolysis functional outcome, and the area under the curve (AUC) and 95% CI was 0.595 (0.555–0.634). The optimal cutoff value of ALI (corresponding to the maximum Youden Index) was 34.522, with a specificity of 0.648 and a sensitivity of 0.520. Youden Index = Sensitivity + 1-Specificity.

Table 3: Association between ALI Q groups and post-stroke functional outcome

Comparison	OR	95% CI	*P*
Q1 Referent	1.00 (Ref)		
Q2 *vs*. Q1	0.530	(0.341–0.824)	0.005
Q3 *vs*. Q1	0.527	(0.338–0.822)	0.005
Q4 *vs*. Q1	0.487	(0.310–0.767)	0.002
Higher ALI Q groups			
Q3 *vs*. Q2	0.994	(0.647–1.526)	0.798
Q4 *vs*. Q2	0.920	(0.599–1.413)	0.702
Q4 *vs*. Q3	0.925	(0.603–1.421)	0.722

Note: Model adjusted for: age, gender, smoke and alcohol, hypertension, diabetes, atrial fibrillation, coronary heart disease, large vessel occlusion, TOAST group, time from onset to admission, antiplatelet therapy, anticoagulation therapy, triglyceride and LDL-C. OR: odds ratio; CI: confidence interval; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LDL-C: low-density lipoprotein cholesterol; ALI: Advanced Lung Cancer Inflammation Index.

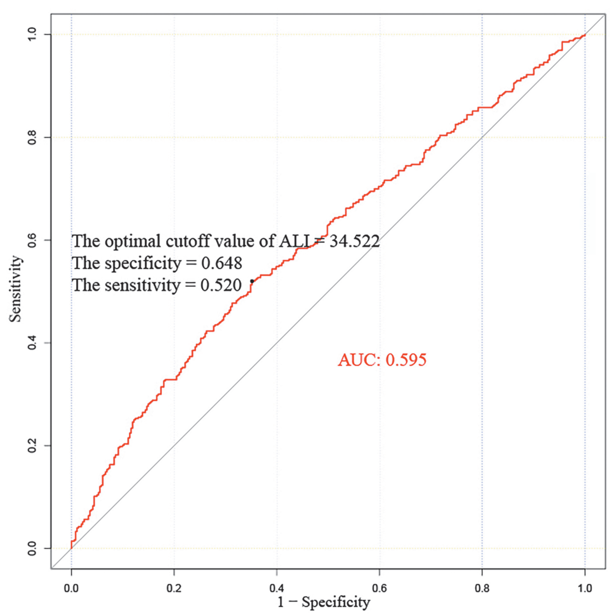

Figure 4: Predictive value of ALI for non-excellent post-thrombolysis functional outcome.

Discussion

Our research suggested that ALI could be linked to the functional outcomes in AIS patients treated with IVT, based on data from three stroke centers. The decreased levels of ALI might be associated with post-thrombolysis non-excellent outcome in AIS patients. These associations remained significant even after adjusting for potential confounding factors in various models. The results of RCS analyses supply evidence to support the non-linear J-shaped association of ALI with non-excellent post-thrombolysis functional outcome. The research indicated that ALI could be a valuable clinical biomarker for predicting non-excellent functional outcomes following intravenous thrombolysis in AIS patients.

ALI, which consists of BMI, ALB, and NLR, serves as an indicator that integrates inflammation as well as nutrition, and offers comprehensive assessment of status[22–24]. BMI was reported to be associated with mortality and recurrent stroke events in stroke patients, according to cohort studies and meta-analyses[25–27]. A study indicated that decreased levels of ALB were associated with increased NIHSS scores at admission and poor prognosis at discharge and 3 months in AIS patients[28]. A meta-analysis showed that decreased serum ALB levels may be related to post-thrombolysis cognitive impairment[29]. One research found that NLR could anticipate cerebral edema and clinical worsening early after reperfusion therapy in stroke[30]. In addition, NLR might be related to post-thrombolysis delirium[31]. Our previous study indicated that NLR might be able to predict post-thrombolysis early neurological outcomes in AIS patients[32]. ALI merges the strengths of BMI, ALB, and NLR in AIS. To date, several researches explored the relationship between the levels of ALI and cerebrovascular disease. According to the study based on the National Health and Nutrition Examination Survey, higher levels of ALI are associated with lower all-cause mortality in stroke survivors[33]. What is more, the data from the Medical Information Mart for Intensive Care-IV database suggests a possible negative relationship between the ALI and all-cause mortality in AIS patients[34]. ALI might serve as a practical and independent prognostic indicator of long-term mortality in patients with spontaneous intracerebral hemorrhage[35]. However, research conducted previously has not concentrated on AIS patients treated with intravenous thrombolysis. The results of our study showed the relationship between ALI and post-thrombolysis 3-month outcome in AIS patients.

It is important to admit that our research has certain drawbacks that need to be identified and addressed in the future investigations. Firstly, while stroke is a disorder with multiple genetic and environmental components, some unknown confounders might still contribute to its pathogenesis, as they were not collected. Secondly, the inherent design restrictions make it a difficult task to deduce causality between ALI and functional outcomes in AIS patients receiving IVT, requiring further validation through larger prospective studies. Thirdly, given that our research was conducted solely on Chinese patients, the correlation between ALI levels and functional outcomes in AIS patients receiving IVT may not extend to non-Chinese populations. In spite of the aforementioned limitations, this marks the first attempt to examine the relationship between ALI levels and the functional outcomes of AIS patients receiving IVT.

In conclusion, our study identified a nonlinear and negative relationship between the ALI and 3-month non-excellent post-thrombolysis functional outcome. ALI may be a conveniently accessible and advantageous biomarker for AIS patients treated with intravenous thrombolysis. To confirm the relationship stated above, more research should be conducted in the future.

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Authors' contributions

All authors contributed substantively to the work reported, both in its conception, study design, execution, data acquisition, analysis, and interpretation, and/or across all these areas. They were involved in drafting, revising, or critically reviewing the manuscript; approved the final version for publication; and agreed to be accountable for all aspects of the work.

Human ethics and consent to participate declarations

The study was approved by the Ethics Committee of Affiliated Hospital of Nantong University (2022-K145-01), Nantong Third People's Hospital, Affiliated Nantong Hospital 3 of Nantong University (EK2021026), and Nanjing First Hospital, Nanjing Medical University (2019-695). The research was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from participants or their legal representatives.

Disclosure of artificial intelligence (AI) use

All authors declare that no AI was used in the writing and publication of this article.

Conflict of interest statement

All the authors declare that there is no conflict of interest.

Consent for publication

All the authors consent to the publication of identifiable details, which can include figures and data details within the text to be published by *Translational Neurology and Neurosurgery*.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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