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Interaction analysis of CONUT score and NLR in predicting functional outcomes after mechanical thrombectomy

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Abstract

Background: This study investigates the prognostic value of the Controlling Nutritional Status (CONUT) score and its relationship with systemic inflammation, measured by the Neutrophil-to-Lymphocyte Ratio (NLR), in patients with acute ischemic stroke (AIS) treated with mechanical thrombectomy (MT). Specifically, we aimed to determine whether NLR acts as a mediator or an effect modifier in the relationship between malnutrition and poor outcomes. *Methods:* This retrospective cohort study analyzed 470 AIS patients undergoing MT. Malnutrition was assessed by the CONUT score, and inflammation was evaluated by NLR upon admission. These assessments were used to investigate their association with the primary outcome, which was poor functional status defined as modified Rankin Scale scores 3 to 6 at 90 days. Multivariable logistic regression, interaction analysis, and exploratory mediation analysis were performed to explore the relationships between malnutrition, inflammation, and functional outcomes. *Results:* Of 470 patients, 57.2% had poor outcomes. The CONUT score was identified as a robust independent predictor of poor prognosis (OR = 1.66, 95% CI: 1.43–1.93, P < 0.001). Mediation analysis revealed that NLR did not significantly mediate the effect of the CONUT score on patient outcomes (P > 0.05). However, a significant synergistic interaction was observed between the CONUT score and NLR (P for interaction = 0.034). Specifically, the risk of poor outcome associated with higher CONUT scores was markedly greater in patients with high inflammatory levels compared to those with low inflammatory levels. Adding CONUT significantly improved the predictive accuracy of the baseline model, with the AUC increasing from 0.785 to 0.842 (P < 0.001).
Conclusions: Malnutrition (high CONUT score) is a strong predictor of poor outcomes after MT. Importantly, systemic inflammation modifies rather than mediates this risk, meaning that it influences the severity of risk without being the direct cause, which supports a synergistic double-hit effect in which malnutrition and inflammation jointly exacerbate patient outcomes. Joint assessment of immuno-nutritional status helps identify high-risk patients who may benefit from intensive management.

Keywords: Acute Ischemic Stroke; Mechanical Thrombectomy; Malnutrition; CONUT score; Neutrophil-to-lymphocyte ratio; Prognosis.

INTRODUCTION

Acute ischemic stroke (AIS) is a leading cause of disability and death worldwide.[1]Mechanical thrombectomy (MT) has become the standard treatment for large-vessel occlusion stroke and substantially improves recanalization rates[2]; however, approximately half of patients with AIS still experience disability or death within three months after reperfusion therapy.[3] Limited functional recovery after recanalization is often attributable to post-ischemic pathophysiological processes, including reperfusion injury and insufficient metabolic reserves, which can result in blood–brain barrier disruption, cerebral

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edema, and hemorrhagic transformation.[4] An increasing body of evidence indicates that patient-level factors, particularly nutritional status and systemic inflammatory responses, may also play an important role in post-stroke functional outcomes.[5] Clinical observations have demonstrated that malnutrition is relatively common at hospital admission among patients with AIS and is frequently associated with a higher risk of adverse outcomes and limited functional recovery.[6,7]

The Controlling Nutritional Status (CONUT) score provides a convenient and objective measure of malnutrition by integrating serum albumin, cholesterol, and lymphocyte count, thereby reflecting malnutrition-related immune suppression and metabolic dysfunction.[8] Previous studies have shown that a high CONUT score, indicative of undernutrition, is independently associated with poorer 3-month outcomes in patients with stroke.[9] Similarly, systemic inflammation plays a critical role in ischemia–reperfusion injury[10]; an elevated neutrophil-to-lymphocyte ratio (NLR), a readily available index of inflammatory status, correlates with larger infarct size and is associated with an increased risk of neurological disability, hemorrhagic complications, and mortality after AIS.[11]

Observational studies further suggest that both malnutrition and excessive inflammatory responses may aggravate endothelial and neuronal injury[12,13] and clinical data indicate that reduced serum albumin and cholesterol levels in malnourished patients are associated with increased blood–brain barrier permeability and a higher incidence of hemorrhagic transformation.[14] Although malnutrition and inflammatory status are each closely associated with adverse stroke outcomes, their interrelationship in shaping clinical outcomes has not yet been clearly defined. Therefore, this study evaluated the prognostic value of the CONUT score in a cohort of patients with AIS treated with mechanical thrombectomy and analyzed the role of NLR in the association between malnutrition and clinical outcomes, focusing on its mediating or effect-modifying role, in order to clarify the relevant features of nutritional status and systemic inflammation in stroke outcomes and to provide a basis for integrated risk stratification in acute stroke patients.

METHODS

Study population

From January 2020 to December 2023, we retrospectively enrolled patients with acute ischemic stroke (AIS) who underwent mechanical thrombectomy (MT) at three hospitals in Wuxi, China (Approval No. MR-32-24-055045). The inclusion criteria were as follows: (1) diagnosis of AIS meeting the diagnostic criteria of the Guidelines for the Early Management of Patients with AIS (2019 edition)[2] and confirmed by cranial computed tomography (CT) or magnetic resonance imaging; (2) meeting the European Stroke Organization—European Society for Minimally Invasive Neurological Therapy[15] guidelines for MT in AIS and having received complete MT; and (3) availability of complete clinical and laboratory data upon admission. The exclusion criteria were: (1) incomplete baseline data; (2) final diagnosis of non-stroke; (3) transient ischemic attack (TIA); (4) severe hepatic or renal dysfunction, or malignant tumors with a life expectancy <3 months; and (5) loss to follow-up at 90 days. Initially, a total of 485 patients were screened. Fifteen patients were excluded according to the prespecified exclusion criteria (incomplete baseline data, non-stroke final diagnosis or TIA, severe hepatic or renal dysfunction or advanced malignancy, and/or loss to 90-day follow-up), leaving 470 patients for the final analysis. Based on the modified Rankin Scale (mRS) score at 90 days after MT, patients were categorized into a good prognosis group (mRS score 0–2) and a poor prognosis group (mRS score 3–6). Eligible patients were consecutively screened during the study period to minimize selection bias. The 90-day mRS was assessed via outpatient visits or structured telephone interviews.

Data collection and definitions

Baseline demographic and clinical characteristics were collected including age, sex, and medical history such as hypertension, diabetes mellitus, atrial fibrillation, smoking, and alcohol consumption. Procedural details recorded included the onset-to-recanalization time and the degree of reperfusion assessed by the modified Thrombolysis in Cerebral Infarction score, mTICI. For subgroup analyses, cut-off values were prespecified based on clinical relevance and commonly used thresholds in acute ischemic stroke research, including a baseline NIHSS

score of 16 and an onset-to-recanalization time of 240 minutes. Laboratory data were obtained from fasting venous blood samples collected within 24 hours of admission which included neutrophils, lymphocytes, serum albumin, total cholesterol, fibrinogen, and fasting blood glucose. The Controlling Nutritional Status score, CONUT, was calculated based on serum albumin, total lymphocyte count, and total cholesterol levels. This score ranges from 0 to 12 where higher scores indicate worse nutritional status. The Neutrophil-to-Lymphocyte Ratio, NLR, was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

Statistical analysis

Statistical analyses were performed using Python (version 3.9) and R (version 4.3.1). Data completeness was assessed prior to analysis; a complete-case analysis was conducted for the primary regression models, as patients with missing key baseline data were excluded during the screening process. Continuous variables were summarized as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Categorical variables were presented as counts and percentages. Between-group comparisons were conducted using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables, as appropriate. Multivariable logistic regression was used to identify independent predictors of poor 90-day functional outcome, with adjustment for clinically relevant covariates and potential confounders. To evaluate whether systemic inflammation modified the association between malnutrition and outcome, an interaction term (CONUT × NLR) was introduced into the regression model. Additional exploratory analyses were conducted as robustness checks, including random forest–based feature importance assessment and mediation analysis. Receiver operating characteristic (ROC) curves were generated to evaluate model discrimination. Sensitivity analyses were performed using alternative NLR specifications (original, log-transformed, and winsorized values) with bootstrap resampling. All tests were two-sided, and a P value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics and comparison of clinical parameters between prognostic groups in AIS patients treated with mechanical thrombectomy

A total of 470 patients were included in the final analysis. Based on the 90-day functional outcomes, 201 patients (42.8%) were classified into the good prognosis group (mRS ≤2), while 269 patients (57.2%) were in the poor prognosis group (mRS >2). Patients with a poor prognosis were significantly older (median 71 vs. 66 years, P < 0.001) and had a higher prevalence of hypertension (P = 0.036) compared to the good prognosis group. Regarding stroke severity and treatment, the poor prognosis group exhibited significantly higher baseline NIHSS scores (median 18 vs. 12, P < 0.001) and a lower rate of successful recanalization (mTICI 2b–3: 86.2% vs. 95.0%, P = 0.003). Notably, markers of nutritional status and inflammation differed between the two groups. Patients with poor outcomes had higher CONUT scores (median 4 vs. 3, P < 0.001) and slightly higher NLR levels (median 8.5 vs. 8.0, P = 0.037). Detailed comparisons of baseline characteristics are presented in Table 1.

Multivariable logistic regression analysis for predictors of poor prognosis

To identify factors associated with poor functional outcomes at 90 days, a multivariable logistic regression analysis was performed (Table 2). Variables with P < 0.10 in univariable analyses and those considered clinically relevant, including age, sex, hypertension, atrial fibrillation, baseline NIHSS score, onset-to-recanalization time, successful recanalization (mTICI 2b–3 vs 0–2a), fasting blood glucose, NLR, and CONUT score, were entered into the model. After adjustment for these covariates, the CONUT score was independently associated with poor outcome; each 1-point increase in CONUT was associated with higher odds of poor outcome (OR = 1.66, 95% CI: 1.43–1.93, P < 0.001). Baseline NIHSS score (OR = 1.22, 95% CI: 1.17–1.29, P < 0.001) and fasting blood glucose (OR = 1.12, 95% CI: 1.05–1.21, P < 0.001) were also independently associated with poor outcome. Successful recanalization (mTICI 2b–3) was associated with lower odds of poor outcome (OR = 0.17, 95% CI: 0.06–0.42, P < 0.001). NLR did not reach statistical significance

Table 1: Baseline characteristics of study population

Characteristic	All Patients (n=470)	Good Outcome (mRS ≤2)	Poor Outcome (mRS >2)	P value
n	470	201	269	
Age, years, median (IQR)	68.0 [57.0,75.0]	66.0 [56.0,74.0]	71.0 [59.0,77.0]	<0.001
Sex, n (%)				0.999
Female	139 (29.6)	59 (29.4)	80 (29.7)	
Male	331 (70.4)	142 (70.6)	189 (70.3)	
Hypertension, n (%)				0.036
No	143 (30.4)	72 (35.8)	71 (26.4)	
Yes	327 (69.6)	129 (64.2)	198 (73.6)	
Diabetes mellitus, n (%)				0.139
No	340 (72.3)	153 (76.1)	187 (69.5)	
Yes	130 (27.7)	48 (23.9)	82 (30.5)	
Atrial fibrillation, n (%)				0.205
No	304 (64.7)	137 (68.2)	167 (62.1)	
Yes	166 (35.3)	64 (31.8)	102 (37.9)	
Current/former smoking, n (%)				0.641
No	350 (74.5)	147 (73.1)	203 (75.5)	
Yes	120 (25.5)	54 (26.9)	66 (24.5)	
Alcohol consumption, n (%)				0.999
No	393 (83.6)	168 (83.6)	225 (83.6)	
Yes	77 (16.4)	33 (16.4)	44 (16.4)	
Baseline NIHSS score, median (IQR)	16.0 [11.0,19.0]	12.0 [8.0,17.0]	18.0 [14.0,21.0]	<0.001
Onset-to-recanalization time, min, median (IQR)	240.0 [180.0,360.0]	240.0 [180.0,360.0]	240.0 [180.0,352.5]	0.093
Successful recanalization (mTICI 2b-3), n (%)	423 (90.0)	191 (95.0)	232 (86.2)	0.003
Intravenous thrombolysis, n (%)				0.342
No	291 (61.9)	119 (59.2)	172 (63.9)	
Yes	179 (38.1)	82 (40.8)	97 (36.1)	
CONUT score, median (IQR)	4.0 [3.0,5.0]	3.0 [2.0,4.0]	4.0 [3.0,5.0]	<0.001
Prognostic nutritional index (PNI), median (IQR)	42.4 [39.4,45.6]	43.8 [41.2,46.4]	41.1 [37.9,44.6]	<0.001
Neutrophil-to-lymphocyte ratio (NLR), median (IQR)	8.2 [5.2,13.3]	8.0 [5.4,13.6]	8.5 [5.2,13.3]	0.037
Fibrinogen, g/L, median (IQR)	2.7 [2.2,3.2]	2.7 [2.2,3.3]	2.6 [2.2,3.2]	0.458

Note: Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. Successful recanalization was defined as mTICI 2b–3. P values were calculated using the Mann–Whitney U test for continuous variables and the χ^2 test (or Fisher's exact test, as appropriate) for categorical variables. Subcategories are indented. IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Infarction; CONUT, Controlling Nutritional Status.

Table 2: Multivariable logistic regression analysis of factors associated with poor outcome

Variable	Odds Ratio (OR)	95% CI	P Value
CONUT (per point increase)	1.66	1.43-1.93	<0.001
Age (per year)	1.01	0.99-1.03	0.330
Sex (Female vs Male)	1.26	0.74-2.14	0.386
Hypertension (yes vs no)	1.16	0.68-1.97	0.597
Atrial fibrillation (yes vs no)	1.42	0.83-2.41	0.197
NIHSS (per point)	1.22	1.17-1.29	<0.001
Onset-to-recanalization time (per 60 min)	0.99	0.94-1.06	0.493
Successful recanalization (mTICI 2b–3 vs 0–2a)	0.17	0.06-0.42	<0.001
Glucose (per mmol/L increase)	1.12	1.05-1.21	<0.001
NLR (per unit increase)	1.01	0.99-1.03	0.063

Odds ratios were estimated using a multivariable logistic regression model including age, sex, hypertension, atrial fibrillation, baseline NIHSS score, CONUT score, neutrophil-to-lymphocyte ratio (NLR), onset-to-recanalization time (per 60 min), fasting blood glucose, and successful recanalization (mTICI 2b–3). Successful recanalization was defined as mTICI 2b–3, with unsuccessful recanalization (mTICI 0–2a) as the reference category. Poor outcome was defined as a modified Rankin Scale (mRS) score of 3–6 at 90 days after stroke. OR, odds ratio; CI, confidence interval; CONUT, Controlling Nutritional Status; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Infarction; mRS, modified Rankin Scale; NLR, neutrophil-to-lymphocyte ratio.

in the multivariable model (OR = 1.01, 95% CI: 0.99–1.03, P = 0.063). Detailed results are shown in Table 2.

Distribution of functional outcomes stratified by nutritional Status: Comparison of 90-day mRS scores across CONUT categories

In the cohort of 470 patients with AIS treated with MT, functional outcomes at 90 days were stratified by nutritional status into three groups: Normal (CONUT 0–1), Mild Malnutrition (CONUT 2–4), and Severe Malnutrition (CONUT ≥5). Patients in the Severe Malnutrition group demonstrated a significantly higher proportion of poor prognosis (mRS >2) and mortality (mRS 6) compared to the Normal and Mild groups. Conversely, the rate of functional independence (mRS ≤2) progressively decreased with worsening nutritional status. The overall shift in the distribution of mRS scores towards unfavorable outcomes was statistically significant across the three groups (P < 0.01). Consistent with the baseline characteristics, a higher CONUT score was strongly associated with an increased likelihood of poor functional recovery. See Figure 1 for the detailed distribution of mRS scores.

Interaction analysis of CONUT score and NLR: Synergistic effect of malnutrition and inflammation

To further explore the biological mechanism underlying the poor prognosis, an interaction analysis was conducted between the CONUT score and systemic inflammation (NLR). The multivariable logistic regression analysis revealed a significant interaction between nutritional status and inflammatory burden (P for interaction < 0.05). As visualized in Figure 2, the association between the CONUT score and the predicted probability of a poor outcome (mRS >2) was significantly modified by the NLR level. In patients with a high inflammatory burden (High NLR), the risk of poor prognosis increased sharply with worsening nutritional status (indicated by the steep red line). Conversely, in patients with a low inflammatory burden (Low NLR), the impact of the CONUT score on prognosis was relatively attenuated (indicated by the flatter blue line). This diverging pattern suggests that systemic inflammation acts as a significant effect modifier, amplifying the adverse consequences of malnutrition in patients with AIS treated with MT.

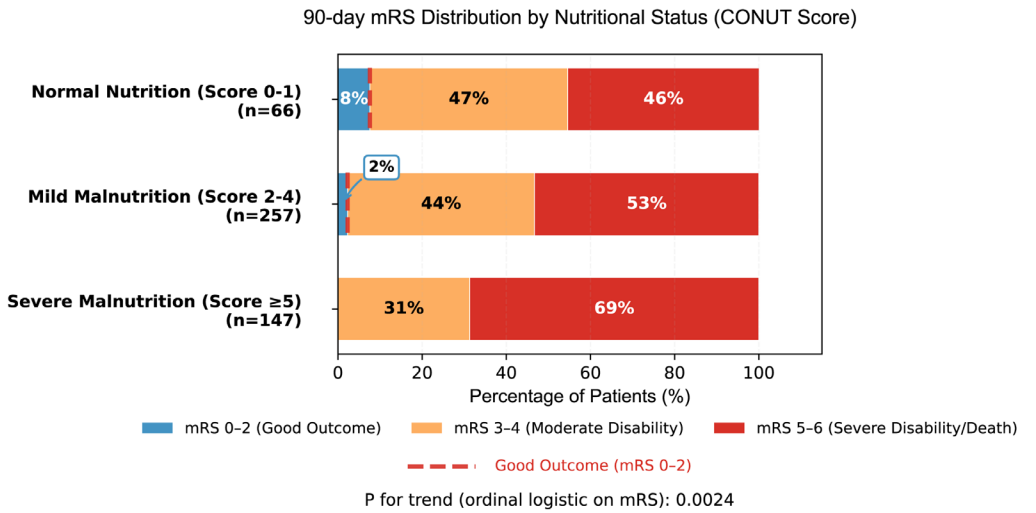

Figure 1. Distribution of 90-day functional outcomes (modified Rankin Scale [mRS] scores) stratified by nutritional status (CONUT score).

Note: The stacked bar chart illustrates the shift in functional outcomes across three nutritional categories: Normal Nutrition (CONUT score 0–1), Mild Malnutrition (CONUT score 2–4), and Severe Malnutrition (CONUT score ≥5). Functional outcomes are grouped into good outcome (mRS 0–2), moderate disability (mRS 3–4), and severe disability or death (mRS 5–6). The dashed red line marks the proportion of patients with a good outcome across the groups. There was a significant shift toward unfavorable outcomes as the severity of malnutrition increased (P for trend = 0.0024). Percentage may not sum to 100% due to rounding.

Abbreviations: CONUT, Controlling Nutritional Status; mRS, modified Rankin Scale.

Predictive value of nutritional and inflammatory markers for 90-day poor prognosis: ROC curves of CONUT score, NLR, and combined models

The predictive capacity of the CONUT score for 90-day adverse prognosis was evaluated in patients with AIS undergoing MT. The ROC curve analysis revealed that the CONUT score alone had a moderate predictive value, with an AUC of 0.71. While informative, single markers often lack the comprehensive power required for complex clinical scenarios. To improve prognostic accuracy, a multivariable logistic regression model was constructed incorporating age, baseline NIHSS score, mTICI grade, and onset-to-recanalization time as the baseline model (Base Model). This baseline model achieved an AUC of 0.785. Furthermore, a comprehensive model integrating the CONUT score into the baseline clinical variables was developed (Base + CONUT). The predictive performance of this combined model (Model 2) showed improved discrimination compared with both the baseline model and the CONUT score alone, achieving an AUC of 0.842. This significant improvement (paired bootstrap test $P < 0.001$) underscores the utility of integrating immuno-nutritional markers into traditional clinical prediction models to enhance risk stratification. The details of the ROC analysis and the comparative performance of the models are provided in Figure 3.

Subgroup analysis of the association between CONUT score and poor prognosis: Consistent prognostic value across clinical subgroups

To verify the robustness of the main findings, a prespecified subgroup analysis was performed to evaluate the association between the CONUT score and 90-day poor prognosis across various clinically relevant strata. As illustrated in the forest plot (Figure 4), higher CONUT scores were consistently associated with an increased risk of poor outcome across all examined subgroups, including age (<65 vs. ≥65 years), sex (male vs. female), baseline stroke severity (NIHSS <16 vs. ≥16), reperfusion status (mTICI 0–2a vs. 2b–3), and onset-to-recanalization time (<240 vs. ≥240 min). Notably, in the subgroup of patients who achieved successful recanalization (mTICI 2b–3), the CONUT score remained a significant risk factor for poor functional outcome (OR > 1, $P < 0.05$), indicating that impaired nutritional and immunological status may adversely affect functional recovery even after effective vessel reopening. Importantly, no

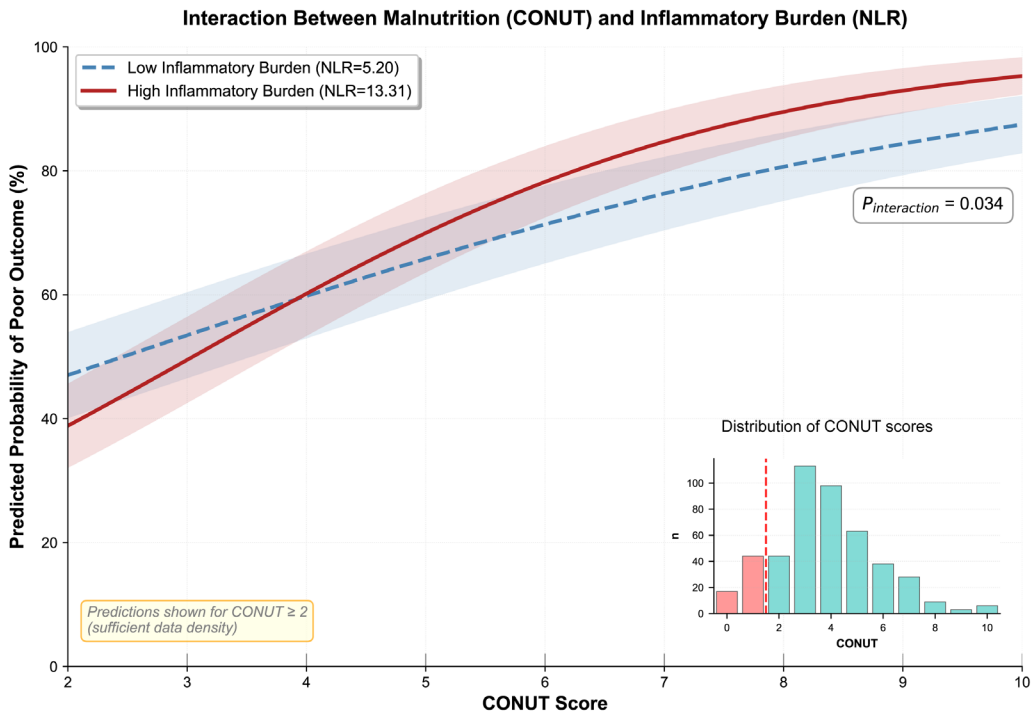

Figure 2. Interaction of systemic inflammation (NLR) on the prognostic value of malnutrition (CONUT).

Note: The plot illustrates the probability of a poor 90-day outcome (mRS > 2) increasing with CONUT scores. The solid red line (high NLR, 13.31) shows a steeper risk increase compared to the dashed blue line (low NLR, 5.20). Shaded regions denote 95% confidence intervals. A significant interaction P for interaction = 0.034 indicates that high inflammation amplifies the adverse effect of malnutrition. The inset histogram shows the distribution of CONUT scores (prediction model limited to scores ≥ 2). Abbreviations: CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio; mRS, modified Rankin Scale.

significant interactions were observed between the CONUT score and any of the stratifying variables (all P for interaction > 0.05), suggesting that the prognostic value of the CONUT score was consistent and independent of these clinical factors. The detailed results of the subgroup analyses are presented in Figure 4.

Interaction analysis and model explainability of CONUT and NLR

To further elucidate the interplay between nutritional status and systemic inflammation, we performed an interaction analysis between the CONUT score and NLR. As presented in Supplementary Table S1, a significant synergistic interaction was consistently observed across multiple sensitivity analyses using original, log-transformed, and winsorized NLR values (all P for interaction < 0.05). Bootstrap validation with 1,000 resamples confirmed the robustness of these findings, with 95% confidence intervals strictly within the positive range, indicating that elevated systemic inflammation amplifies the deleterious prognostic impact of malnutrition. Furthermore, a SHAP (Shapley Additive Explanations) summary plot was generated to interpret the machine learning model and quantify the relative contribution of each feature. As depicted in Supplementary Figure S1, the baseline NIHSS score was the foremost predictor of functional outcome, followed by the CONUT score and NLR. Notably, higher CONUT values consistently corresponded to positive SHAP values (indicating increased risk), thereby corroborating the independent and clinically significant role of immunonutritional status within an explainable AI framework.

DISCUSSION

Among patients with AIS undergoing MT, conventional prognostic assessment has largely relied on clinical severity and reperfusion-related indicators.[16] However, even in cases of successful recanalization, substantial

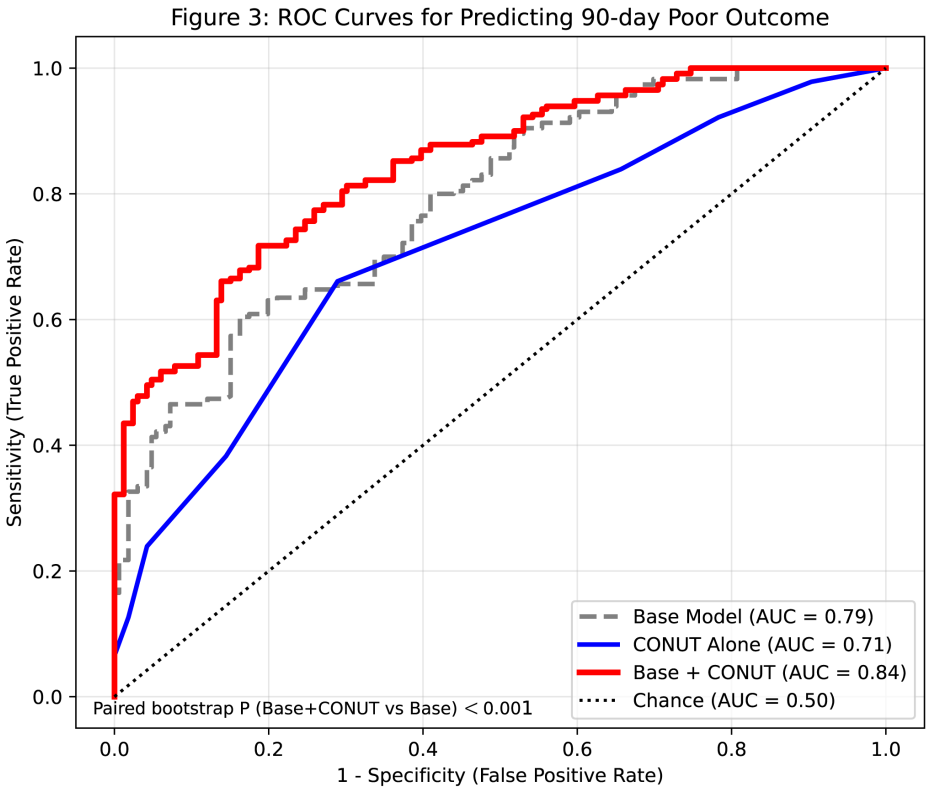

Figure 3. Incremental predictive value of the CONUT score for 90-day poor functional outcome after mechanical thrombectomy.

Note: Receiver operating characteristic (ROC) curves comparing the discriminative performance of different predictive models for 90-day poor functional outcome. The base clinical model (gray dashed line), which included age, baseline NIHSS score, mTICI grade, and onset-to-recanalization time, yielded an area under the curve (AUC) of 0.79. The model including the CONUT score alone showed modest discrimination (blue solid line; AUC = 0.71). Incorporation of the CONUT score into the base model significantly improved predictive performance (red solid line; AUC = 0.84). The diagonal dotted line represents chance-level discrimination (AUC = 0.50). Improvement in model discrimination with the addition of CONUT was assessed using paired bootstrap resampling, demonstrating a statistically significant increase in AUC compared with the base model alone $P < 0.001$. Abbreviations: AUC, area under the curve; CONUT, Controlling Nutritional Status; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Infarction; ROC, receiver operating characteristic.

heterogeneity in long-term functional recovery persists, suggesting that host baseline conditions, beyond vascular factors alone, may play an important role in post-reperfusion recovery.[17] In recent years, immunonutritional impairment and systemic inflammation have been increasingly recognized as being closely associated with stroke prognosis.[18] Nevertheless, in the specific MT population, whether immunonutritional status can provide stable incremental prognostic information beyond traditional clinical and recanalization metrics, and whether inflammatory burden modifies the association between nutritional risk and outcomes, remain insufficiently supported by systematic empirical evidence. In this context, the present study suggests that an immunonutritional perspective may offer complementary information for prognostic stratification in patients undergoing mechanical thrombectomy. Compared with traditional frameworks that primarily depend on stroke severity and reperfusion-related indicators[16], admission immunonutritional status was not only associated with 90-day functional outcomes but also improved risk stratification based on clinical variables. Specifically, CONUT as a single indicator demonstrated moderate predictive performance. When CONUT was incorporated into a baseline model comprising age, baseline NIHSS score, mTICI grade, and onset-to-recanalization time, model discrimination was further enhanced,

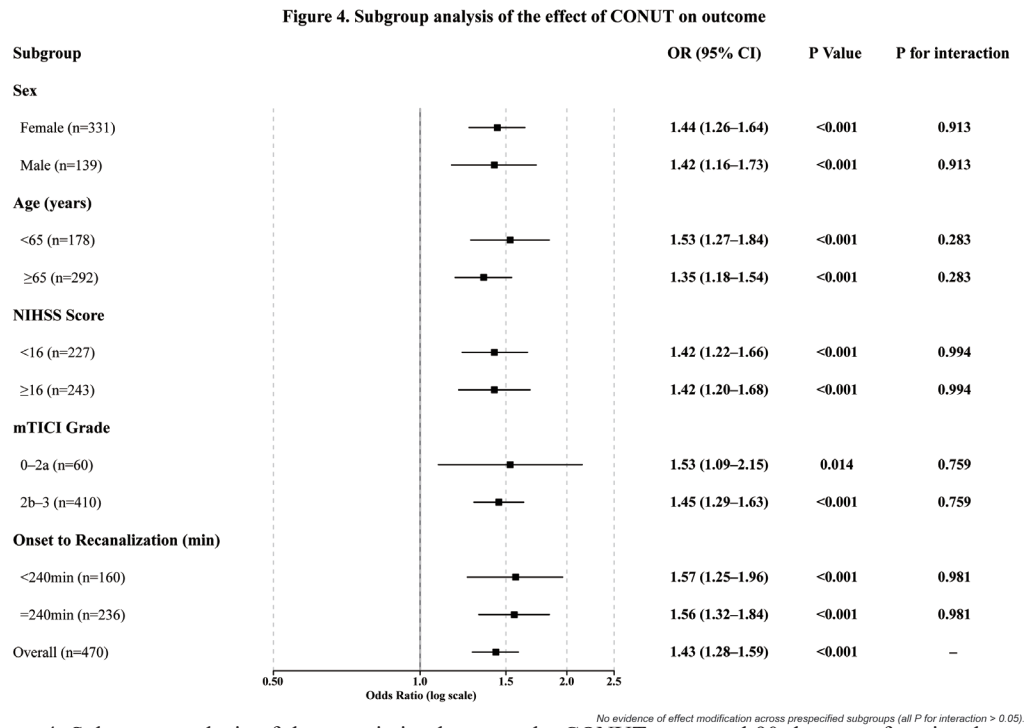

Figure 4. Subgroup analysis of the association between the CONUT score and 90-day poor functional outcome after mechanical thrombectomy.

Note: Forest plot showing the association between the CONUT score and 90-day poor functional outcome across predefined clinical subgroups. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression models adjusted for clinically relevant covariates. Subgroup analyses were performed according to sex, age (<65 vs. ≥65 years), baseline stroke severity (NIHSS <16 vs. ≥16), recanalization status (mTICI 0–2a vs. 2b–3), and onset-to-recanalization time (<240 vs. ≥240 minutes). The vertical solid line indicates an OR of 1.0. values for interaction were derived by including an interaction term between the CONUT score and each subgroup variable in the regression model. No significant effect modification was observed across subgroups (all P for interaction > 0.05), indicating a consistent association between higher CONUT scores and increased risk of poor outcome.

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

with statistical support confirmed by paired bootstrap testing. These findings indicate that, within emergency and stroke center workflows, CONUT, as a rapidly obtainable composite laboratory index, may facilitate early risk stratification and inform management decisions at admission. Importantly, the prognostic value of CONUT remained consistent across multiple clinical subgroups and persisted as a risk factor among patients with successful recanalization (mTICI 2b-3)[19], with no significant effect modification observed across stratification variables. This suggests that the information captured by CONUT is not merely a surrogate for stroke severity or recanalization status, but may instead reflect non-vascular factors such as recovery reserve and susceptibility to complications. Such factors may help explain the clinical observation that a subset of patients experiences unfavorable functional outcomes despite successful reperfusion.[19] From a clinical perspective, a key contribution of this study lies in elucidating the pattern by which inflammatory burden influences the association between nutritional risk and prognosis. Supplementary analyses demonstrated a statistically significant interaction between CONUT and NLR, with consistent results across analyses using raw values, logarithmic transformation, and winsorized data. Moreover, 1,000-iteration bootstrap robustness analyses supported the stability of the interaction direction, with confidence intervals that did not cross zero. Collectively, these findings indicate that the association between nutritional risk and poor outcomes is more pronounced in the presence of elevated inflammatory burden, representing a typical effect-modification relationship rather

than a simple linear additive effect.[20] Accordingly, the combination of high CONUT and high NLR identifies a subgroup of patients at particularly high risk, who may warrant closer monitoring and more integrated management during the peri-procedural and early rehabilitation phases. At the same time, these results argue against treating either CONUT or NLR as a single, isolated intervention target.

Finally, SHAP analysis showed that NIHSS contributed most substantially to model predictions, followed by CONUT and NLR. This pattern aligns with the established clinical understanding that stroke outcomes are primarily driven by the severity of neurological deficits, while also supporting the informational contribution of CONUT within predictive models from an interpretable machine-learning perspective. It should be emphasized that SHAP values reflect feature contributions at the model level rather than causal effects; therefore, they are more appropriately used to illustrate the relative importance and consistency of predictors in outcome prediction, rather than as evidence of causality or underlying pathophysiological mechanisms.

This study is limited by its retrospective, observational design and therefore remains susceptible to selection bias and residual confounding. The generalizability of the findings to external cohorts requires further validation.

In addition, the characterization of immunonutritional status and inflammatory burden relied primarily on baseline CONUT and NLR values at admission, which do not capture dynamic changes during hospitalization. Moreover, additional indicators reflecting inflammatory pathways, metabolic status, or nutritional interventions were not incorporated, limiting further elucidation of underlying biological mechanisms and potential windows for intervention. In addition, although interaction analyses and methodological approaches such as SHAP support risk stratification and incremental predictive gain, they do not constitute causal inference. Whether stratified management targeting this high-risk phenotype can translate into meaningful clinical outcome benefits warrants confirmation in prospective studies.

In conclusion, among patients with acute ischemic stroke undergoing mechanical thrombectomy, the CONUT score provides valuable prognostic information beyond traditional clinical variables, enabling early risk stratification with quantifiable improvements in predictive performance. The inflammatory milieu modifies and amplifies the adverse impact of nutritional risk on outcomes, suggesting that the combined assessment of CONUT and NLR facilitates the identification of a higher-risk composite phenotype. This integrated approach may offer a more actionable framework for peri-procedural monitoring and the allocation of rehabilitation resources.

DISCLOSURE

Ethics: The research protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University (Approval No. MR-32-24-055045). Owing to the retrospective study design and the use of de-identified medical record data without direct patient involvement, the requirement for informed consent was waived.

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

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Conflicts of interest: None

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Supplementary Table S1: Mechanism analysis results
Interaction analysis (CONUT × NLR)

NLR Transformation	Interaction Coefficient (β)	P Value	Bootstrap P Value†	Bootstrap 95% CI
Original NLR	0.0216	0.034	0.002	0.0040 to 0.0552
Log-transformed NLR	0.3220	0.002	<0.001	0.1230 to 0.5965
Winsorized NLR‡	0.0224	0.024	0.008	0.0044 to 0.0558

Note: Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio; mRS, modified Rankin Scale. Analysis Specification: The outcome of interest was defined as poor functional outcome (mRS > 2). Sensitivity analyses were performed on 463 complete cases (7 patients were excluded due to missing data or outliers). Symbols: † Based on 1,000 bootstrap resamples. ‡ Winsorized at the 1st and 99th percentiles to mitigate the influence of outliers. Significance levels: * , ** . Interpretation: The consistent positive interaction coefficients across all sensitivity analyses indicate that the deleterious effect of malnutrition (higher CONUT score) on stroke prognosis is significantly amplified as systemic inflammation (NLR) increases.

Supplementary Figure S1. SHAP summary plot illustrating the relative contributions of clinical variables to 90-day poor functional outcome.
Note: SHAP (Shapley Additive Explanations) summary plot depicting the relative importance and directional effects of individual variables on the prediction of 90-day poor functional outcome. Each point represents an individual patient, with the SHAP value indicating the contribution of a given feature to the model output. Positive SHAP values indicate an increased probability of poor outcome, whereas negative values indicate a decreased probability. Features are ranked in descending order according to their overall importance. Color gradients reflect the original feature values (blue = low, red = high). Baseline NIHSS score showed the greatest contribution to outcome prediction, followed by the CONUT score and neutrophil-to-lymphocyte ratio (NLR), supporting the clinically meaningful roles of nutritional status and systemic inflammation in determining post-thrombectomy functional outcomes. Abbreviations: AF, atrial fibrillation; CONUT, Controlling Nutritional Status; LDL-C, low-density lipoprotein cholesterol; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; SHAP, Shapley Additive Explanations.