

Malnutrition and the Risk of Early Neurological Deterioration in Elderly Patients with Acute Ischemic Stroke

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Background and Purpose: This study aimed to investigate the relationship between malnutrition and early neurological deterioration (END) in elderly patients with acute ischemic stroke in China.

Methods: We used the registry data in the Third Affiliated Hospital of Nantong University and Nanjing Brain Hospital from June 2019 to January 2021. Malnutrition risk was evaluated by controlling nutritional status score (CONUT), geriatric nutritional risk index (GNRI) and prognostic nutritional index (PNI) score, respectively. END was defined as an increment of at least two points in the total NIHSS score within three days after admission. We evaluated the relationship between malnutrition and END with multivariable logistic regression models and reclassification indexes.

Results: A total of 732 elderly patients with first-ever acute ischemic stroke were included in the study. 243 patients developed END. 5.7%, 21.4%, 4.6% patients were classified as moderate to severe malnutrition by CONUT, GNRI and PNI, respectively. Malnutrition was associated with the risk of END for CONUT (odds ratio [OR], 1.210; 95% confidence interval [CI] 1.092–1.341; $P < 0.001$), for GNRI (OR, 0.943; 95% CI, 0.919–0.967; $P < 0.001$), and for PNI (OR, 0.936; 95% CI, 0.908–0.965; $P < 0.001$) in multivariable logistic regression models using the back-ward selection method. The discriminative ability was 0.763 (95% CI, 0.727–0.798) for CONUT, 0.769 (95% CI, 0.733–0.805) for GNRI and 0.769 (95% CI, 0.733–0.805) for PNI after adjusting for confounders. Besides, adding malnutrition indexes into models made the prediction of END more accurate.

Conclusion: Malnutrition was associated with END in elderly Chinese patients with acute ischemic stroke.

Keywords: malnutrition, ischemic stroke, elderly, early neurological deterioration

Introduction

Ischemic stroke is the leading cause of mobility and mortality worldwide.^{1,2} Despite advances in management in the acute stage, early neurological deterioration (END) still occurs in approximately 5–40% of patients with ischemic stroke and is associated with mobility and mortality.^{3,4} Elderly patients make up more than 80% of the ischemic stroke population and have unfavorable clinical outcomes.^{5,6} Previous studies suggested that symptomatic intracranial hemorrhage, malignant vasogenic edema, and older age were associated with END.^{7,8} The increasingly older age at onset of END makes preventing END in elderly patients important.

Malnutrition is frequent in the elderly and causes various complications that affect the prognosis, such as muscle atrophy and immune system suppression.⁹ Stroke patients are more likely to be malnourished due to cognitive impairments and dysphagia.¹⁰ Besides, evaluating nutrition status could be hard in elderly stroke patients for stroke-related symptoms and age-related changes in body composition.^{10,11} Controlling nutritional status score (CONUT)¹² was calculated from serum albumin, lymphocyte count and total cholesterol and was a helpful indicator of malnutrition in

cardiovascular diseases.¹³ Geriatric nutritional risk index (GNRI)¹⁴ was associated with worse prognoses in elderly patients with heart failure using three objective parameters: body height, weight and serum albumin.¹⁵ Prognostic nutritional index (PNI)¹⁶ was calculated from serum albumin and lymphocyte count and could predict postoperative outcome of cancer surgery.¹⁷ Raposeiras Roubín et al integrated three malnutrition tools and found that these tools were associated with poor prognosis in acute coronary syndrome regardless of the malnutrition tools used.¹⁸ Hence, we performed this study to investigate the potential role of malnutrition in elderly patients with acute ischemic stroke with three convenient scores.

Methods

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

Participants

This study was a retrospective analysis of a prospective registry in the Third Affiliated Hospital of Nantong University and Nanjing Brain Hospital from June 2019 to January 2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and their later amendments or comparable ethical standards in the Third Affiliated Hospital of Nantong University and Nanjing Brain Hospital. Due to our retrospective nature, patient consent was waived. Patients' data confidentiality were maintained in the Third Affiliated Hospital of Nantong University and Nanjing Brain Hospital.

Patients were included according to the following criterion: (1) aged ≥ 65 years old; (2) diagnosed as first-ever ischemic stroke with 24 hours of onset; (3) had a brain computed tomography or magnetic resonance imaging scan right before or during hospitalization. Patients were excluded if they: (1) were treated with intravenous thrombolysis or endovascular treatment; (2) early discharge; (3) had no measurement of weight, height, albumin level, lymphocyte count, and total cholesterol level; (4) had a history of malignant tumor, hematological system diseases, severe renal disease, hepatic disease and infectious disease.

Clinical Assessment

Demographic characteristics, vascular risk factors, and radical images were all collected. Laboratory data were routinely collected within 24 hours of hospital admission. Blood pressure was measured immediately after admission. Pneumonia during acute stroke was recorded. Smoking and drinking status were collected using a face-to-face questionnaire. Stroke subtypes were classified according to the trial of ORG 10172 in Acute Stroke Treatment classification (TOAST).¹⁹ Infarct sites were based on the brain computed tomography or magnetic resonance imaging scan right before or during hospitalization.

Definition of END

The baseline stroke severity was assessed with National Instituted of Health Stroke Scale (NIHSS).²⁰ END was defined as an increment of at least two points in the total NIHSS score within three days after admission.^{3,21}

Malnutrition Indexes

CONUT score was derived from the level of total cholesterol, serum albumin, and lymphocyte count and was calculated according to the following formula: albumin (g/dl): ≥ 3.5 (0), 3–3.4 (2), 2.9–2.9 (4), < 2.5 (6), total cholesterol (mg/dl): ≥ 180 (0), 140–179 (1), 100–139 (2), < 100 (3) lymphocyte count ($10^9/l$): ≥ 1.6 (0), 1.2–1.59 (1), 0.8–1.19 (2), < 0.8 (3). Nutritional status was defined according to scores: absent (0–1), mild (2–4), moderate (5–8), severe (9–12) malnutrition.¹²

GNRI score was calculated with the following formula: $1.489 \times \text{serum albumin (g/l)} + 41.7 \times (\text{current weight in kilograms/ideal weight})$. Ideal weight was measured with the Lorenz formulas: height - 100 - $([\text{height} - 150]/4)$ for men and height - 100 - $([\text{height} - 150]/2.5)$ for women. (Current weight in kilograms /ideal weight) was set to 1 when the current weight was greater than the ideal body weight. Nutritional status was classified according to scores: absent (≥ 100), mild (97.50–99.99), moderate (83.50–97.49), and severe (< 83.50) malnutrition.¹⁴

PNI score was calculated using the formula: $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$. Nutritional status was classified according to scores: absent (>38), moderate (35–38), and severe (<35) malnutrition.¹⁶

Statistical Analysis

Continuous variables were presented as mean \pm SD or median (interquartile range, IQR) and compared with *t*-test or Mann–Whitney *U*-test as appropriate. Categorical variables were presented as n (%) and compared with χ^2 test or Fisher exact test as appropriate. Multiple imputations with chain equations were performed to deal with missing values.

Variables were selectively included in logistic regression models to explore the relationship between malnutrition and END in the elderly with acute ischemic stroke. Model 1 was adjusted for age, sex, atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, smoking, and drinking. Model 2 was adjusted for variables with a significance level of < 0.1 in univariable logistic regression analysis using a back-ward selection method except for variables included in the GNRI, CONUT, and PNI scores.

We used receiver operating characteristic curves with variables in model 2 to explore the discrimination of malnutrition indexes. We applied restricted cubic splines with 4 knots (at 5th, 35th, 65th, and 95th percentiles) to explore the pattern of the association between malnutrition indexes and END adjusted for variables in model 2.²² Additionally, we used the net reclassification index and integrated discrimination improvement to estimate the improvement of predictive performance after adding malnutrition indexes into different models.²³

All statistical tests were conducted with R statistical software version 4.1.0. (R Foundation, Vienna, Austria) and a two-sided *P* value < 0.05 was considered to be statistically significant.

Results

A total of 732 elderly patients with first-ever acute ischemic stroke were included in the study. 243 patients developed END within three days after admission (Table 1). 494 (67.5%) patients were male. The median age of patients was 71 [IQR, 67–75] years. 5.7% for CONUT, 21.4% for GNRI, 4.6% for PNI and 2.9% for all three tools were classified as moderate to severe malnutrition, respectively (Table 1, Supplementary Table 1). Compared with patients without END, those with END had a higher risk of malnutrition according to CONUT ($P = 0.002$), GNRI ($P < 0.001$) and PNI score ($P = 0.001$), older age ($P = 0.045$), lower body weight ($P < 0.001$), body mass index ($P < 0.001$), higher systolic blood pressure ($P = 0.001$), higher proportion of diabetes mellitus ($P < 0.001$), hypertension ($P = 0.012$), large-artery atherosclerosis and cardio embolic stroke ($P < 0.001$), lower level of triglyceride ($P = 0.035$), higher level of low-density lipoprotein ($P = 0.041$), fasting plasma glucose ($P < 0.001$), c-reactive protein ($P < 0.001$) and albumin ($P < 0.001$, Table 1).

Malnutrition indexes were associated with END in elderly patients with acute ischemic stroke in univariable logistic regression models (Supplementary Table 2). After adjusting for the potential cofounders, the association remained significant in model 1 (Table 2). Variables included in the model 2 after back-ward selecting were diabetes mellitus, hypertension, c-reactive protein, stroke subtype, homocysteine, triglyceride and body mass index for CONUT (odds ratio [OR], 1.210; 95% confidence interval [CI], 1.092–1.341; $P < 0.001$), for GNRI (OR, 0.943; 95% CI, 0.919–0.967; $P < 0.001$) and for PNI (OR, 0.936; 95% CI, 0.908–0.965; $P < 0.001$, Table 2, Supplementary Table 3).

The discriminative ability was 0.763 (95% CI, 0.727–0.798) for CONUT, 0.769 (95% CI, 0.733–0.805) for GNRI, and 0.769 (95% CI, 0.733–0.805) for PNI score (Figure 1). Furthermore, adding malnutrition indexes to model 2 slightly improved the continuous NRI (CONUT, 0.235; 95% CI, 0.087–0.392; $P = 0.002$; GNRI, 0.293; 95% CI, 0.141–0.445; $P < 0.001$; PNI, 0.219; 95% CI, 0.066–0.372; $P = 0.005$), categorical NRI (CONUT, 0.076; 95% CI, 0.003–0.122; $P = 0.001$ GNRI, 0.078; 95% CI, 0.023–0.132; $P = 0.005$; PNI, 0.086; 95% CI, 0.033–0.139; $P = 0.002$) and IDI (CONUT, 0.014; 95% CI, 0.003–0.024; $P = 0.011$; GNRI, 0.027; 95% CI, 0.014–0.445; $P < 0.001$; PNI, 0.023; 95% CI, 0.011–0.035; $P = 0.005$, Supplementary Table 4).

Multiple-adjusted restricted cubic spline regression showed an ascending trend of CONUT score ($P = 0.025$ for nonlinearity, Figure 2A), a descending trend of GNRI ($P = 0.004$ for nonlinearity, Figure 2B), and PNI score ($P = 0.182$ for nonlinearity, Figure 2C) with the risk of END in elderly patients with acute ischemic stroke.

Table 1 Characteristics of Patients with or Without END

Characteristics	Without END (n = 489)	With END (n = 243)	P value
Age, years	71.0 [67.0, 75.0]	72.0 [67.0, 76.0]	0.045
Male, n (%)	337 (68.9)	157 (64.6)	0.277
Height, cm	165.0 [160.0, 170.0]	167.0 [160.0, 170.0]	0.495
Weight, kg	68.0 [60.0, 75.0]	64.0 [57.8, 70.0]	<0.001
Body mass index, kg/m ²	24.4 [22.5, 26.6]	23.7 [21.5, 25.4]	<0.001
Vascular risk factors, n (%)			
Hypertension	329 (67.3)	186 (76.5)	0.012
Diabetes mellitus	108 (22.1)	94 (38.7)	<0.001
Hyperlipidemia	88 (18.0)	51 (21.0)	0.383
Atrial fibrillation	51 (10.4)	27 (11.1)	0.877
Smoking	153 (31.3)	74 (30.5)	0.884
Drinking	136 (27.8)	66 (27.2)	0.922
Coronary heart disease	48 (9.8)	30 (12.3)	0.359
SBP, mmHg	140.0 [130.0, 160.0]	149.0 [132.0, 160.5]	0.001
DBP, mmHg	84.0 [78.0, 90.0]	85.0 [76.0, 92.5]	0.349
NIHSS, score	7.0 [2.0, 9.0]	6.0 [3.5, 7.0]	0.610
Pneumonia, n (%)	52 (10.6)	34 (14.0)	0.228
Infarct site, n (%)			0.120
Lobe	118 (24.1)	53 (21.8)	
Basal ganglia	131 (26.8)	86 (35.4)	
Tentorium cerebelli	65 (13.3)	27 (11.1)	
Others	175 (35.8)	77 (31.7)	
TOAST, n (%)			0.003
LAA	227 (46.4)	114 (46.9)	
CE	45 (9.2)	28 (11.5)	
SAA	145 (29.7)	81 (33.3)	
SOE	20 (4.1)	14 (5.8)	
SUE	52 (10.6)	6 (2.5)	
Laboratory data			
Total cholesterol, mmol/L	4.5 [3.7, 5.3]	4.5 [3.9, 5.4]	0.541
Triglyceride, mmol/L	1.4 [1.0, 2.0]	1.3 [1.0, 1.8]	0.035
Low-density lipoprotein, mmol/L	2.3 [1.8, 2.9]	2.5 [1.9, 3.0]	0.041
High-density lipoprotein, mmol/L	1.3 [1.1, 1.5]	1.3 [1.1, 1.6]	0.461
Fasting plasma glucose, mmol/L	5.4 [5.0, 7.1]	6.5 [5.4, 8.0]	<0.001
Homocysteine, μmol/L	13.0 [11.0, 19.0]	14.0 [11.2, 19.0]	0.063
White blood cell, 10 ⁹ /L	9.7 [7.7, 12.4]	10.1 [8.2, 12.6]	0.107
C-reactive protein, mg/L	4.0 [1.0, 8.0]	6.0 [2.9, 11.5]	<0.001
Albumin, g/L	40.3 [37.7, 42.9]	39.3 [36.1, 41.8]	<0.001
Lymphocyte count, 10 ⁹ /L	1.6 [1.2, 2.1]	1.6 [1.2, 2.0]	0.090
Uric acid, μmol/L	318 [251, 390]	325 [262.5, 398]	0.208
Malnutrition, n (%)			
CONUT			0.002
Absent	229 (46.8)	104 (42.8)	
Mild	243 (49.7)	114 (46.9)	
Moderate	15 (3.1)	19 (7.8)	
Severe	2 (0.4)	6 (2.5)	
GNRI			<0.001
Absent	367 (75.1)	150 (61.7)	
Mild	45 (9.2)	13 (5.3)	
Moderate	73 (14.9)	71 (29.2)	
Severe	4 (0.8)	9 (3.7)	

(Continued)

Table 1 (Continued).

Characteristics	Without END (n = 489)	With END (n = 243)	P value
PNI			0.001
Absent	473 (96.7)	225 (92.6)	
Moderate	13 (2.7)	7 (2.9)	
Severe	3 (0.6)	11 (4.5)	

Abbreviations: CE, cardio-embolism; CONUT, controlling nutritional status score; DBP, diastolic blood pressure; GNRI, geriatric nutritional risk index; LAA, large-artery atherosclerosis; NIHSS, National Institute of Health Stroke Scale; PNI, prognostic nutritional index; SAA, small-vessel occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; SBP, systolic blood pressure.

Table 2 Multivariable Analysis of Malnutrition Indexes and the Risk of END

Indexes	Variables	Model 1 Adjusted OR (95% CI)	P value	Model 2 Adjusted OR (95% CI)	P value
CONUT	Absent	Reference		Reference	
	Mild	1.035 (0.743–1.444)	0.839	1.124 (0.786–1.610)	0.523
	Moderate	2.862 (1.361–6.112)	0.006	4.361 (1.951–9.983)	<0.001
	Severe	7.93 (1.738–55.716)	0.014	16.222 (3.337–119.164)	0.001
	Per one-point increment	1.139 (1.036–1.253)	0.007	1.210 (1.092–1.341)	<0.001
GNRI	Absent	Reference		Reference	
	Mild	0.748 (0.371–1.417)	0.391	0.758 (0.358–1.514)	0.449
	Moderate	2.477 (1.672–3.677)	<0.001	2.741 (1.803–4.182)	<0.001
	Severe	6.026 (1.864–23.096)	0.004	13.510 (3.898–56.472)	<0.001
	Per one-point increment	0.950 (0.927–0.972)	<0.001	0.943 (0.919–0.967)	<0.001
PNI	Absent	Reference		Reference	
	Moderate	1.058 (0.376–2.751)	0.91	1.524 (0.517–4.22)	0.426
	Severe	8.016 (2.41–36.267)	0.002	20.507 (5.615–100.645)	<0.001
	Per one-point increment	0.946 (0.92–0.973)	<0.001	0.936 (0.908–0.965)	<0.001

Notes: Model 1, adjusted for age, sex, atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, smoking and drinking. Model 2, adjusted for variables finally included in the model after back-ward selection.

Abbreviations: CI, confidence interval; CONUT, controlling nutritional status score; GNRI, geriatric nutritional risk index; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; PNI, prognostic nutritional index.

Discussion

In the present study, we investigated the relationship between malnutrition and END in elderly patients with first-ever acute ischemic stroke using easily calculated screening scores. Our findings suggested that malnutrition was prevalent in elderly stroke patients and associated with an increased risk of END in the acute phase. Besides, adding malnutrition indexes into models made the prediction of END more accurate.

Previous studies reported that END was associated with poor prognosis in patients with acute ischemic stroke.^{4,24,25} Geng et al conducted a retrospective analysis in three stroke units and reported that 32% of patients with ischemic stroke experienced END.²⁶ Identifying predictors of END at an early stage could improve the acute management of stroke patients. The prevalence of malnutrition varies from 6 to 62.5% in stroke patients owing to different tools and measuring time.²⁷ Zhang et al reported that 1.95–5.89% of patients with acute ischemic stroke had a moderate to severe malnutrition risk.²⁸ Due to the inclusion criterion of the elderly population only, the proportion of END (33.2%) and moderate to severe malnutrition risk (4.6–21.4%) in our study were higher than in previous reports.

CONUT, GNRI, and PNI scores are convenient tools that might be more suitable for stroke patients because of objective indicators. Zhang et al performed a nationwide study and found that malnutrition was associated with long-term mobility and mortality in acute ischemic stroke.²⁸ The FOOD trial proved that ischemic stroke patients who were malnourished at admission had poor six-month prognoses.²⁹ It is recommended that enteral diets, nutritional

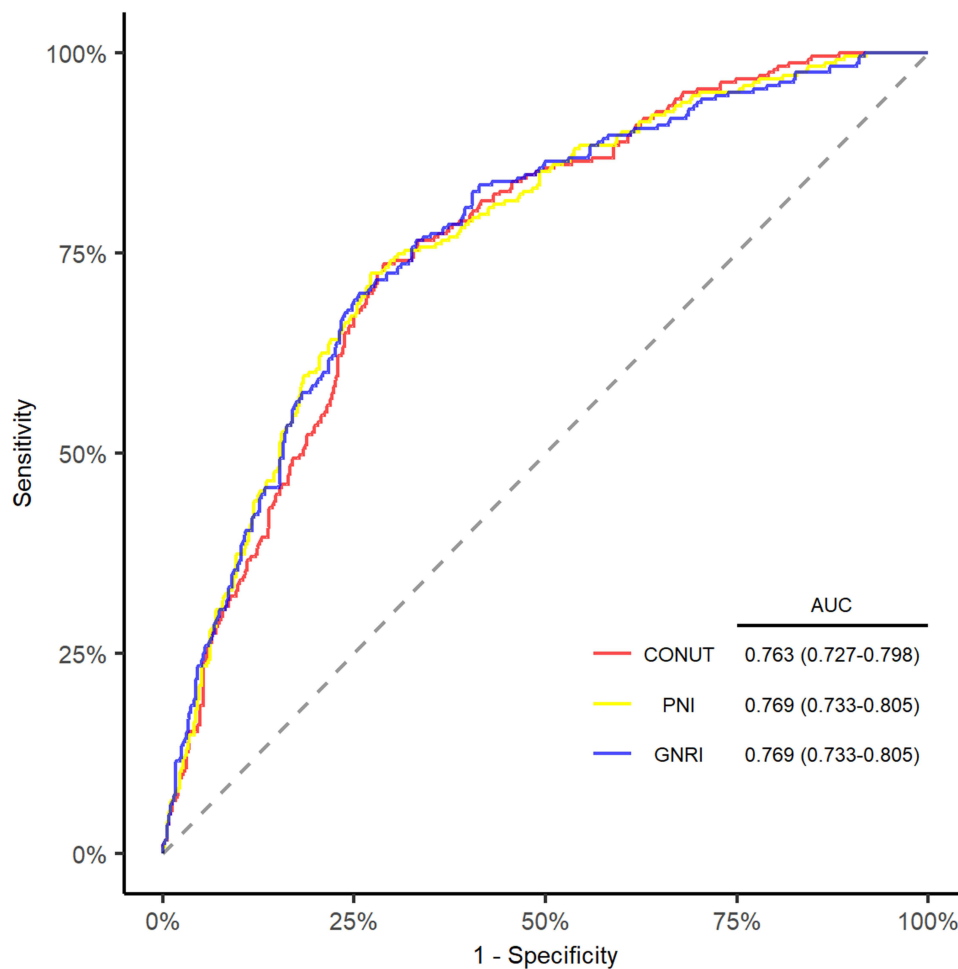


Figure 1 ROC Curve and AUC for the prediction of END with 3 Malnutrition Scores.

Abbreviations: AUC, area under curve, CONUT, controlling nutritional status score; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index, ROC, receiver operating characteristic curve.

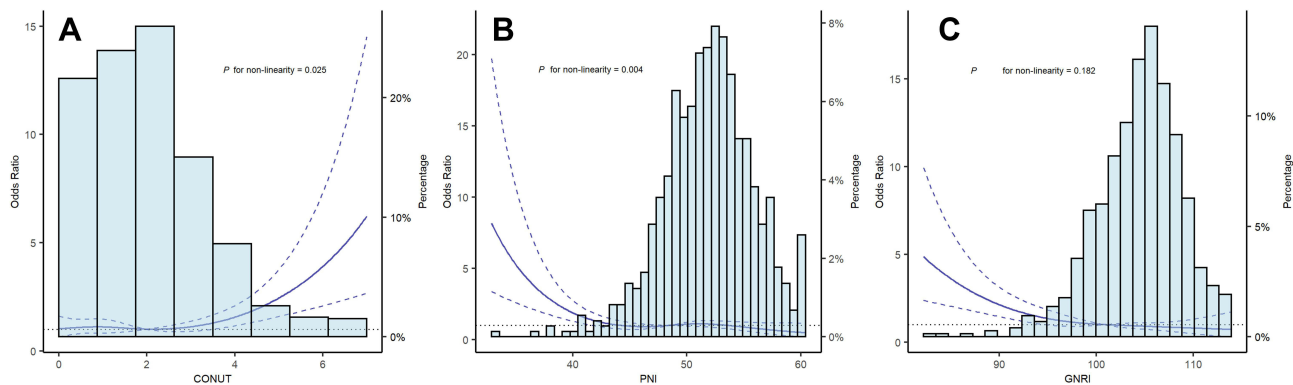


Figure 2 Restricted cubic spline with 4 knots (at fifth, 35th, 65th, 95th percentiles) for 3 malnutrition scores adjusted for variables included in model 2. The solid line indicated the odds ratio and the dashed lines indicated the corresponding 95% confidence interval. Subfigure (A), CONUT; subfigure (B), PNI; subfigure (C), GNRI.

Abbreviations: CONUT, controlling nutritional status score; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index.

supplements, and nasogastric tubes should be supplied for patients with malnutrition or those at malnutrition risk.³⁰ Daily nutrition supplements could improve nutrition and functional outcomes in the elderly population, and protein-based diets might reduce malnutrition risk in the elderly.^{31,32} To our knowledge, the association between malnutrition scores and END in acute ischemic stroke has yet to be investigated.

The components in the formula of scores might explain the relationship between malnutrition and END in elderly stroke patients. Previous studies showed that inflammatory response played an important role in the progression and early neurological outcome of acute ischemic stroke.³³ Lymphocyte counts are a neuroprotective marker and could promote neurological improvements.³⁴ Kim et al found that lower lymphocyte counts were linked to poor functional outcomes in the long term.³⁵ Duan et al suggested that neutrophil-to-lymphocyte independently predicted SICH and functional outcomes in large vessel occlusion ischemic stroke.³⁶ Serum albumin is a neuroprotective protein with multifunctional properties.³⁷ Belayev et al found that human albumin therapy improved neurological function and reduced the swelling and infarction volume in stroke animal models.³⁸ Dziedzic et al showed that lower albumin increased the risk of poor outcomes three months after ischemic stroke.³⁷ In our study, patients with END had lower levels of albumin, which represented the reduced neuroprotective state and might lead to the occurrence of END in patients with acute ischemic stroke. Total cholesterol remained a controversial indicator in ischemic stroke. In our study, total cholesterol was not significant in the univariate analysis, and the CONUT score, which was the only score that included total cholesterol in the formula, had an average performance among the three malnutrition tools. Ryu et al investigated the association between serum lipid profile and END and found that hyperlipidemia increased END risk in acute ischemic stroke.³⁹ However, Zhao et al found that patients with lower total cholesterol levels had poor outcomes in acute ischemic stroke and suggested that physicians should make suitable treatments based on cholesterol levels.⁴⁰

In addition, our study found that diabetes mellitus, c-reactive protein, homocysteine, triglyceride, and stroke subtype were significantly associated with END in elderly stroke patients. Giroto et al found that diabetes mellitus was an independent predictor of END in acute ischemic stroke treated with endovascular treatment.⁴¹ Huang et al found that admission glucose increased END risk in females with acute ischemic stroke.⁴² Duan et al explored the relation between c-reactive protein and END in stroke patients and reported that c-reactive protein level was independently related to END.⁴³ Kwon et al reanalyzed data from the CAIST trial and found that elevated homocysteine increased the risk of END.⁴⁴ Cui et al performed a secondary analysis of the INTRECIS trial and suggested that TOAST classification was associated with END in patients with anterior circulation stroke.⁴⁵ Zhang et al conducted a prospective cohort study and found that hypertriglyceridemia was related to an increased risk of END in acute ischemic stroke.⁸

Our study has several limitations. Firstly, it was a retrospective study without a younger age group, which might generate sampling biases. Secondly, the definition of END varied across different studies, and we applied the acknowledged definition of END reported in a systematic review.^{3,21} Thirdly, the mechanism of END would differ between patients receiving reperfusion therapy and patients without receiving reperfusion therapy. We excluded patients receiving reperfusion therapy to better assess the association between malnutrition and END. Fourth, although we limited the sampling time of blood parameters to 24 hours at admission, the variation of sampling time might still generate biases. Finally, limited by the study design, we could not compare the performance of malnutrition scores to other scores that were collected in a prospective study design.

In conclusion, our study found that malnutrition was associated with the risk of END in elderly Chinese patients with acute ischemic stroke and recommended the GRNI score for screening malnutrition in elderly patients with acute ischemic stroke because of the higher AUC value and better reclassification indexes. We suggested that clinical physicians should routinely screen malnutrition in elderly stroke patients and identify patients who might benefit from nutritional supplementation. However, we still warranted further investigations into potential mechanisms and whether nutrition intervention might mitigate the risk of END.

Disclosure

The authors have declared no conflicts of interest with respect to the authorship or publication of this article.

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