Controlling Nutritional Status score for predicting 3-mo functional outcome in acute ischemic stroke

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Running head: CONUT score predicts short-term stroke outcome

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Authors' contribution

HN, TN, and NH designed the study. HN and TN wrote the manuscript draft. HN, TN, SA, NK, JK, RS, MA, HU, and KO collected the data. HN, TN, and NH performed statistical analysis. HN, TN, NH, SA, NK, JK, RS, MA, HU, KO, and HM took part in the discussion of the results, and revised the manuscript, and approved the final version.

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Abstract

Background: Malnutrition is an independent risk factor for poor outcomes in patients with acute ischemic stroke (AIS). However, the indicator of malnutrition has not yet been established. We investigated the relationship between the Controlling Nutritional Status (CONUT) score, a useful prognostic measure of malnutrition in patients with cardiovascular diseases and malignant tumors, and functional outcomes in patients with AIS.

Methods: Patients with AIS (n = 264, 70 ± 12 years old) were consecutively evaluated within 7 days of stroke onset. The CONUT score was calculated from the serum albumin, total peripheral lymphocyte count, and total cholesterol; a CONUT score of 5–12 was defined as malnutrition. Poor functional outcome was defined as a modified Rankin Scale score of 3–6 at 3 months.

Results: Of the total cohort, 230 patients (87.1%) were assessed. The patients with poor functional outcome (n = 85) were older, had a lower body mass index; higher frequency of atrial fibrillation, chronic heart failure, and anemia; and lower frequency of dyslipidemia and a current smoking status. In addition, the CONUT score and National Institutes of Health Stroke Scale score at admission were significantly higher for the patients with poor functional outcome. After multivariate analysis, adjusted for baseline characteristics, a CONUT score of 5–12 was found to be independently associated with poor outcome (odds ratio: 4.15, 95% confidence interval: 1.52–11.67, $p = 0.005$).

Conclusions: The CONUT score at admission could be a useful prognostic marker of 3-month functional outcomes in patients with AIS.

Keywords: acute ischemic stroke, Controlling Nutritional Status score, nutrition, prognosis

Introduction

Malnutrition has been reported to be an independent risk factor for morbidity and mortality in patients with acute ischemic stroke (AIS) [1-3]. The prevalence of malnutrition after AIS has been reported to range from 8% to 34% [3]. In addition, malnourished patients, at admission, showed a higher frequency of pneumonia, other infections, gastrointestinal bleeding, and bedsores than nourished patients [1, 3]. Nutritional management is, therefore, a non-pharmacological approach toward improving patient outcomes. Nutritional interventions may prevent weight loss and enhance the muscle strength and quality of life of malnourished patients with stroke [4, 5]. Therefore, it is important to evaluate the nutritional status of patients with AIS, at admission.

Nutritional status has been assessed by measuring serum albumin levels, body mass index (BMI), and the Geriatric Nutritional Risk Index (GNRI) [6-9]. Anemia has also been considered as a measure of nutritional status, and has been associated with stroke mortality [10]. However, a universally-accepted indicator of malnutrition has not yet been established. Recently, the prognostic value of the Controlling Nutritional Status (CONUT) score in malnutrition has been demonstrated in patients with cardiovascular diseases and malignant tumors [11-13]. The CONUT was initially proposed as a screening tool for identifying undernutrition in hospitalized patients [14]. The CONUT score, which is an index calculated from the serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, is a convenient and cost-effective method of predicting outcomes objectively and comprehensively. However, it is unclear whether the CONUT score is also useful for the prognosis of stroke outcomes. Thus, the aim of the present study was to elucidate the association of the CONUT score with 3-month functional outcomes in patients with AIS. In addition, we investigated the association between the CONUT score and other nutritional indicators, such as the GNRI and anemia, and compared their utility as predictors of stroke outcomes.

Methods

Study population

This was a single-center, hospital-based retrospective study, involving consecutive patients with AIS hospitalized in the Hiroshima University. A total of 311 patients with AIS were admitted to our hospital between March 2011 and March 2017. Of these, 25 patients were excluded from the analysis because their pre-morbid modified Rankin Scale (mRS) score was 3 or more, and 22 patients were excluded because of the lack of sufficient data to calculate the CONUT scores. Therefore, the final study population comprised of 264 patients. The clinical and demographic data are shown in Table 1. The mean age of the participants was 71 ± 12 years, and 93 (35.2%) were female. Regarding the nutritional status, the BMI was 22.8 ± 4.0, serum albumin concentration was 3.8 ± 0.6 g/dL, median GNRI was 98 (89–103), and the median CONUT score was 2 (1–4).

Ethics approval

This study complies with the Declaration of Helsinki for investigations involving humans, and the study protocol was approved by the Ethics Committee of the Hiroshima University Hospital.

Assessment of clinical characteristics

Participants were considered eligible if they had been hospitalized within one week of stroke onset. Ischemic stroke was defined as the sudden onset of acute neurologic deficits, with evidence of acute infarction on brain computed tomography or magnetic resonance imaging. The severity of the event was assessed according to the National Institutes of Health Stroke Scale (NIHSS) score. Stroke subtypes were classified according to the criteria laid down by the Trial of ORG 10172 in Acute Stroke Treatment classification [15]. The following clinical characteristics were recorded at admission: age; sex; BMI; classical vascular risk factors including hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic heart failure (CHF), daily alcohol intake (> 40 g), and smoking habit; and laboratory findings, including those from hematological, biochemical, and coagulation tests.

Hypertension was diagnosed if the patient's blood pressure was ≥ 140/90 mm Hg or if the patient had received any anti-hypertensive medication. Dyslipidemia was diagnosed if the patient had low-density lipoprotein cholesterol ≥ 140 mg/dL, triglycerides ≥ 150 mg/dL, and/or high-density lipoprotein cholesterol < 40 mg/dL, according to the criteria established by the Japan Atherosclerosis Society [16], or if the patient had a medical history of hypercholesterolemia. Diabetes mellitus was diagnosed based on fasting serum glucose ≥ 126 mg/dL, serum glucose ≥ 200 mg/dL on two random measurements, and

HbA1c ≥ 6.5%, or a medical history of diabetes mellitus. Patients were classified as either current or non-current smokers. Atrial fibrillation was diagnosed when a previous electrocardiography (ECG) or ECG performed on admission revealed atrial fibrillation. Diagnosis of CHF was made in accordance with the judgment of the attending physician. Anemia was defined according to the World Health Organization criteria as a hemoglobin concentration < 13 g/dL in men and < 12 g/dL in women [17].

CONUT scores

The CONUT scores were calculated as described in Table 2. The range of the CONUT scores is 0 to 12; an individual with a normal nutritional status is awarded a score of 0, and higher scores indicate a worse nutritional status. According to the original stratification of the CONUT score (normal nutritional status: 0–1, mild malnutrition: 2–4, moderate: 5–8, and severe: 9–12) [14], a CONUT score of 5–12 was used to define malnutrition (moderate or severe) in this study. We obtained the blood samples for the CONUT score within 2 days after admission. We also used the GNRI as an indicator of nutritional status, based on a previous study [9]. The GNRI was calculated as follows: [(1.489 × serum albumin (g/L)) + (41.7 × (current body weight/ideal body weight)] [18]. The ideal body weight was defined as the value calculated from the height and a BMI of 22 [18]. The current body weight/ideal body weight ratio was set to 1 when the patient's body weight exceeded the ideal body weight [19]. Malnutrition was defined by a low GNRI (< 92), as previously described [9].

The primary outcome was evaluated from the 3-month functional status: poor outcome was defined as a mRS score of 3–6, and good outcome as an mRS score of 0–2.

Statistical Analysis

Categorical variables have been presented as numbers and percentages, and continuous variables as means with standard deviation (SD) or median (interquartile range). The statistical significance of intergroup differences was assessed using χ^2 tests for categorical variables, and Student's t-tests or Mann-Whitney U tests for continuous variables. To obtain the cutoff CONUT score for discriminating between patients with and without primary outcome, receiver operating characteristic (ROC) curves were constructed. Correlation analyses between the CONUT score and the GNRI or hemoglobin levels were performed using Pearson's linear regression. Univariate logistic analyses were performed to identify each nutritional indicator (CONUT score of 5–12, low GNRI, and anemia). The factors listed in Table 2, except for laboratory findings and stroke subtypes, were selected for poor stroke outcome using a backward selection procedure, with a p value > 0.10 as the exclusion criterion for the likelihood ratio test. Next, a multivariate logistic analysis was performed for each nutritional indicator (CONUT score, low GNRI, and anemia) and other baseline factors that remained as predictors of poor stroke outcome after the above-mentioned stepwise procedure. In all analyses, $p < 0.05$ was considered statistically significant. All analyses were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient outcomes

Of the 264 patients, 230 (87.1%) were assessed for the functional outcomes 3 months after stoke onset (Fig. 1). Of these, 85 patients (37.0%) had poor outcomes. These patients were significantly older, had a lower BMI, and higher frequency of atrial fibrillation, CHF, and anemia than those with good outcomes; patients with poor outcomes also had a lower frequency of dyslipidemia and a current smoking status than those with good outcomes. The patients with poor outcomes exhibited severe neurological deficits at admission.

Laboratory findings

Among the laboratory findings, the serum albumin concentration, total cholesterol level, lymphocyte count, and hemoglobin level were lower in the patients with poor outcomes than in those with good outcomes. The patients with poor outcomes were more malnourished than those with good outcomes, based on their CONUT scores and GNRI. The optimal cutoff of the CONUT score for predicting poor outcomes in patients was ≥ 4, with a sensitivity of 45.9%, specificity of 85.5%, and an area under the ROC curve of 0.702. As the CONUT score became higher, the proportion of patients with poor functional outcome increased, and the poor functional outcome exceed 70% when the score was 5–8 or 9–12 (Fig. 2).

CONUT scores and patient outcomes

There was a significant correlation between the CONUT scores and GNRI and hemoglobin levels (both $p < 0.001$) (Fig. 3). Univariate logistic analyses showed that a CONUT score of 5–12, low GNRI (< 92), and anemia were significantly associated with poor outcome at 3 months (odds ratio [OR]: 6.05, 95% confidence interval [CI]: 2.95–13.09, $p < 0.001$; OR: 3.32, 95% CI: 1.85–6.02, $p < 0.001$; and OR: 2.01, 95% CI: 1.16–3.48, $p = 0.012$, respectively). Other baseline characteristics such as BMI, current smoking, and NIHSS score at admission were associated with a poor stroke outcome. Multivariate logistic regression analysis for each nutritional indicator (CONUT score of 5–12, low GNRI [< 92], and anemia), adjusted for BMI, current smoking, NIHSS score at admission, and nutritional indicators (CONUT score of 5–12, low GNRI [< 92], and anemia) revealed that only a CONUT score of 5–12 was independently associated with the 3-month functional outcome (OR: 4.15, 95% CI: 1.52–11.67, $p = 0.005$) (Table 3). The cutoff CONUT score of ≥ 4, adopted based on the ROC analysis, was also independently associated with the 3-month functional outcome (OR: 4.70, 95% CI: 2.00 – 11.33, $p < 0.001$).

Discussion

In the present study, we showed that the CONUT score is significantly associated with a poor 3-month functional outcome in patients with AIS, adjusted for age, sex, initial stroke severity, and other confounding factors. In addition, the CONUT score might be superior to other nutritional indicators, such as GNRI and anemia, as a predictor of stroke outcome.

Each factor constituting the CONUT score was also significantly associated with poor functional outcome in univariate analysis, and these biochemical markers have been described as prognostic factors of poor outcomes in patients with ischemic stroke. Several clinical studies have demonstrated that lower serum albumin levels in patients with stroke are associated with poor outcomes [6-8]. Experimental studies have also shown that human albumin therapy significantly improves neurological status in animal models of acute stroke [20]. Serum albumin is a multifunctional protein that plays neuroprotective roles in ischemic stroke, such as reducing the hematocrit level, influencing erythrocyte aggregation, and constituting a major antioxidant defense against oxidizing agents [20-22]. These findings may explain the effect of serum albumin on the stroke outcome.

A higher total cholesterol level is a well-known risk factor for coronary heart disease, but the association between total cholesterol level and stroke is still unclear. Previous studies have found that a high total cholesterol level is a risk factor for ischemic stroke [23, 24], and a lower total cholesterol level is an independent predictor of poor outcomes in ischemic stroke [25]. In the present study, patients with poor outcomes had a lower total cholesterol level than those with good outcomes.

The immune and inflammatory responses following stroke are known to play a major role in ischemic brain pathobiology [26]. As systemic inflammatory markers, white blood cells and their subtypes, including neutrophils and lymphocytes, are known to mediate the response during cerebrovascular diseases. Lower lymphocyte counts have been associated with a poor functional outcome after AIS, whereas higher white blood cell and neutrophil counts have been associated with a greater severity of stroke at admission in patients with AIS [27]. Recently, the neutrophil-to-lymphocyte ratio has been suggested to be an easily measurable systemic inflammation marker, and a useful predictor of poor prognosis in ischemic stroke [28, 29]. In the present study, lower lymphocyte counts were a significant factor associated with the 3-month poor outcome in AIS, which is consistent with previous reports.

Previous reports have demonstrated that nutritional status indicators, such as albumin levels and BMI, are the prognostic factors in AIS [8]. The GNRI, calculated from serum albumin concentration and body weight, has also been reported to be a useful predictor of poor functional improvements in geriatric patients with stroke [9]. In addition, we previously reported that anemia at admission was associated with stroke mortality, independent of underweight status [10]. Indeed, albumin level, BMI, and anemia were associated with poor outcome in univariate analysis. However, the present study shows that low GNRI and anemia were not significantly associated with poor outcome in multivariate analysis. Therefore, our study reveals that only the CONUT score is a valuable independent predictor of poor prognosis 3 months after stroke onset. Each of its three components, including albumin level, total cholesterol, and lymphocyte count have been shown to evaluate the different aspects of the nutritional condition: albumin for impaired protein metabolism, total cholesterol level for lipid metabolism, and lymphocyte count for immunity [11]. Therefore, the CONUT score is more comprehensive and appropriate for assessing malnutrition, and a stronger prognostic factor for poor 3-month outcomes in AIS than other indicators. Previous studies have found that a CONUT score ≥ 5 was associated with a moderate or severe malnutrition status [14]. In the present study, the cutoff CONUT score of 5–12 was a valuable prognostic factor for a 3-month functional outcome. On the other hand, from this study, the optimal cutoff CONUT score for predicting poor outcomes in patients was ≥ 4, based on ROC analysis. A CONUT score of 4–12 was also significantly associated with a poor 3-month poor outcome, as well as a CONUT score of 5–12.

This study has several limitations. Firstly, this was a single-center study, with a small sample size, which might have resulted in selection bias. However, the baseline characteristics of the patients were not remarkably different from those previously reported in a large Japanese stroke registry study [30]. Thus, we conclude that the selection bias did not influence our study greatly. Secondly, due to its retrospective nature, this study lacked detailed nutritional information, including dietary intake, weight change, and physical examination findings regarding muscle and fat. Thus, we could not evaluate the nutritional status more comprehensively by using indicators such as the Subjective Global Assessment [31] and the Mini Nutritional Assessment [32]. In addition, because of the usual nutritional management in all patients, we could not investigate how the outcomes are changed by active nutritional interventions for patients with a worse nutritional status. Further larger prospective studies are needed to clarify the findings of the present study.

In conclusion, the CONUT score offers an objective and comprehensive assessment of nutritional status, and is easily obtained from blood examinations in standard clinical settings. Thus, assessment of nutrition using the CONUT score at admission could be a useful prognostic marker of the 3-month functional outcomes in patients with AIS.

References

[1] Dávalos A, Ricart W, Gonzalez-Huix F, Soler S, Marrugat J, Molins A, Suñer R, Genís D (1996) Effect of malnutrition after acute stroke on clinical outcome. Stroke 27:1028-1032. https://doi.org/10.1161/01.STR.27.6.1028

[2] Gariballa SE, Parker SG, Taub N, Castleden M (1998) Nutritional status of hospitalized acute stroke patients. Br J Nutr 79:481-487. https://doi.org/10.1079/BJN19980085

[3] FOOD Trial Collaboration (2003) Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. Stroke 34:1450-1456. https://doi.org/10.1161/01.STR.0000074037.49197.8C

[4] Ha L, Hauge T, Spenning AB, Iversen PO (2010) Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: a randomized, controlled trial. Clin Nutr 29:567-573. https://doi.org/10.1016/j.clnu.2010.01.011

[5] Nishioka S, Wakabayashi H, Nishioka E, Yoshida T, Mori N, Watanabe R (2016) Nutritional improvement correlates with recovery of activities of daily living among malnourished elderly stroke patients in the convalescent stage: a cross-sectional study. J Acad Nutr Diet 116:837-843. https://doi.org/10.1016/j.jand.2015.09.014

[6] Dziedzic T, Slowik A, Szczudlik A (2004) Serum albumin level as a predictor of ischemic stroke outcome. Stroke 35:e156-e158. https://doi.org/10.1161/01.STR.0000126609.18735.be

[7] Babu MS, Kaul S, Dadheech S, Rajeshwar K, Jyothy A, Munshi A (2013) Serum

albumin levels in ischemic stroke and its subtypes: correlation with clinical outcome. Nutrition 29:872-875. https://doi.org/10.1016/j.nut.2012.12.015

[8] Kimura Y, Yamada M, Kakehi T, Itagaki A, Tanaka N, Muroh Y (2017) Combination of low body mass index and low serum albumin level leads to poor functional recovery in stroke patients. J Stroke Cerebrovasc Dis 26:448-453. https:doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.008

[9] Kokura Y, Maeda K, Wakabayashi H, Nishioka S, Higashi S (2016) High nutritional-related risk on admission predicts less improvement of functional independence measure in geriatric stroke patients: a retrospective cohort study. J Stroke Cerebrovasc Dis 25:1335-1341. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.01.048

[10] Kubo S, Hosomi N, Hara N, Neshige S, Himeno T, Takeshima S, Takamatsu K, Shimoe Y, Ota T, Maruyama H, Ohtsuki T, Kuriyama M, Matsumoto M (2017) Ischemic stroke mortality is more strongly associated with anemia on admission than with underweight status. J Stroke Cerebrovasc Dis 26:1369-1374. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.02.016

[11] Iwakami N, Nagai T, Furukawa TA, Sugano Y, Honda S, Okada A, Asaumi Y, Aiba T, Noguchi T, Kusano K, Ogawa H, Yasuda S, Anzai T, NaDEF investigators (2017) Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. Int J Cardiol 230:529-536. https://doi.org/10.1016/j.ijcard.2016.12.064

[12] Iseki Y, Shibutani M, Maeda K, Nagahara H, Ohtani H, Sugano K, Ikeya T,

Muguruma K, Tanaka H, Toyokawa T, Sakurai K, Hirakawa K (2015) Impact of the preoperative Controlling Nutritional Status (CONUT) score on the survival after curative surgery for colorectal cancer. PLoS One 10:e0132488. https://doi.org/10.1371/journal.pone.0132488

[13] Toyokawa T, Kubo N, Tamura T, Sakurai K, Amano R, Tanaka H, Muguruma K, Yashiro M, Hirakawa K, Ohira M (2016) The pretreatment Controlling Nutritional Status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study. BMC Cancer 16:722. https://doi.org/10.1186/s12885-016-2696-0

[14] Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, Rodrígues F, Fernández G (2005) CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 20:38-45.

[15] Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 24:35-41. https://doi.org/10.1161/01.STR.24.1.35

[16] Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M, Japan Atherosclerosis Society (JAS) Committee for Epidemiology and Clinical Management of Atherosclerosis (2007) Diagnostic criteria for dyslipidemia. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb 14:155-

158.

[17] World Health Organization (1968) Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 405:5-37.

[18] Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L, Aussel C (2005) Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 82:777-783.

[19] Yamada K, Furuya R, Takita T, Maruyama Y, Yamaguchi Y, Ohkawa S, Kumagai H (2008) Simplified nutritional screening tools for patients on maintenance hemodialysis. Am J Clin Nutr 87:106-113.

[20] Belayev L, Liu Y, Zhao W, Busto R, Ginsberg MD (2001) Human albumin therapy of acute ischemic stroke. Marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. Stroke 32:553-560. https://doi.org/10.1161/01.STR.32.2.553

[21] Reinhart WH, Nagy C (1995) Albumin affects erythrocyte aggregation and sedimentation. Eur J Clin Invest 25:523-528. https://doi.org/ 10.1111/j.1365-2362.1995.tb01739.x

[22] Halliwell B (1998) Albumin: an important extracellular antioxidant? Biochem Pharmacol 37:569-571. https://doi.org/10.1016/0006-2952(88)90126-8

[23] Lindenstrøm E, Boysen G, Nyboe J (1994) Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. BMJ 309:11-15. https://doi.org/10.1136/bmj.309.6946.11

[24] Benfante R, Yano K, Hwang LJ, Curb JD, Kagan A, Ross W (1994) Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men. Stroke 25:814-820. https://doi.org/10.1161/01.STR.25.4.814

[25] Zhao W, An Z, Hong Y, Zhou G, Guo J, Zhang Y, Yang Y, Ning X, Wang J (2016) Low total cholesterol level is the independent predictor of poor outcomes in patients with acute ischemic stroke: a hospital-based prospective study. BMC Neurol 16:36. https://doi.org/10.1186/s12883-016-0561-z

[26] Kim JY, Park J, Chang JY, Kim SH, Lee JE (2016) Inflammation after ischemic stroke: the role of leukocytes and glial cells. Exp Neurobiol 25:241-251. https://doi.org/10.5607/en.2016.25.5.241

[27] Kim J, Song TJ, Park JH, Lee HS, Nam CM, Nam HS, Kim YD, Heo JH (2012) Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction. Atherosclerosis 222:464-467. https://doi.org/10.1016/j.atherosclerosis.2012.02.042

[28] Celikbilek A, Ismailogullari S, Zararsiz G. (2014) Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. J Clin Lab Anal 28:27-31. https://doi.org/10.1002/jcla.21639

[29] Qun S, Tang Y, Sun J, Liu Z, Wu J, Zhang J, Guo J, Xu Z, Zhang D, Chen Z, Hu F, Xu X, Ge W (2017) Neutrophil-To-Lymphocyte Ratio Predicts 3-Month Outcome of Acute Ischemic Stroke. Neurotox Res 31:444-452. https://doi.org/10.1007/s12640-017-9707-z

[30] Kamouchi M, Matsuki T, Hata J, Kuwashiro T, Ago T, Sambongi Y, Fukushima Y, Sugimori H, Kitazono T; FSR Investigators (2011) Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: the Fukuoka Stroke Registry. Stroke 42:2788-2794. https://doi.org/10.1161/STROKEAHA.111.617415
[31] Yamauti AK, Ochiai ME, Bifulco PS, de Araújo MA, Alonso RR, Ribeiro RH, Pereira-Barretto AC (2006) Subjective global assessment of nutritional status in cardiac patients. Arq Bras Cardiol 87:772-777. http://dx.doi.org/10.1590/S0066-782X2006001900014
[32] Aggarwal A, Kumar A, Gregory MP, Blair C, Pauwaa S, Tatooles AJ, Pappas PS, Bhat G (2013) Nutrition assessment in advanced heart failure patients evaluated for ventricular assist devices or cardiac transplantation. Nutr Clin Pract 28:112-119. https://doi.org/10.1177/0884533612457948

Figure legends

Fig. 1 Flow chart of patient selection. mRS, modified Rankin Scale; CONUT, Controlling Nutritional Status

Fig. 2 Distribution of acute ischemic stroke patients with modified Rankin Scale score (mRS) at 3 months for each Controlling Nutritional Status (CONUT) score. The percentage of patients with a mRS score of 0–2 was decreased with the increases in the CONUT score, and an mRS of 3–6 exceeded 70% when the CONUT score was 5–8 or 9–12; mRS of 3–6 (open columns) and mRS of 0–2 (black columns)

Fig. 3 Scatter plot of Controlling Nutritional Status (CONUT) score with Geriatric Nutritional Risk Index (GNRI, a) and hemoglobin (Hb) levels (b). Linear associations were observed between the CONUT score and GNRI ($R^2 = 0.54$) and Hb levels ($R^2 = 0.32$)

Fig.1

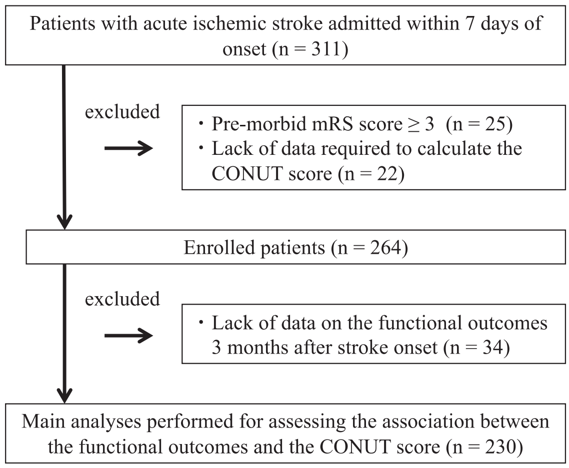
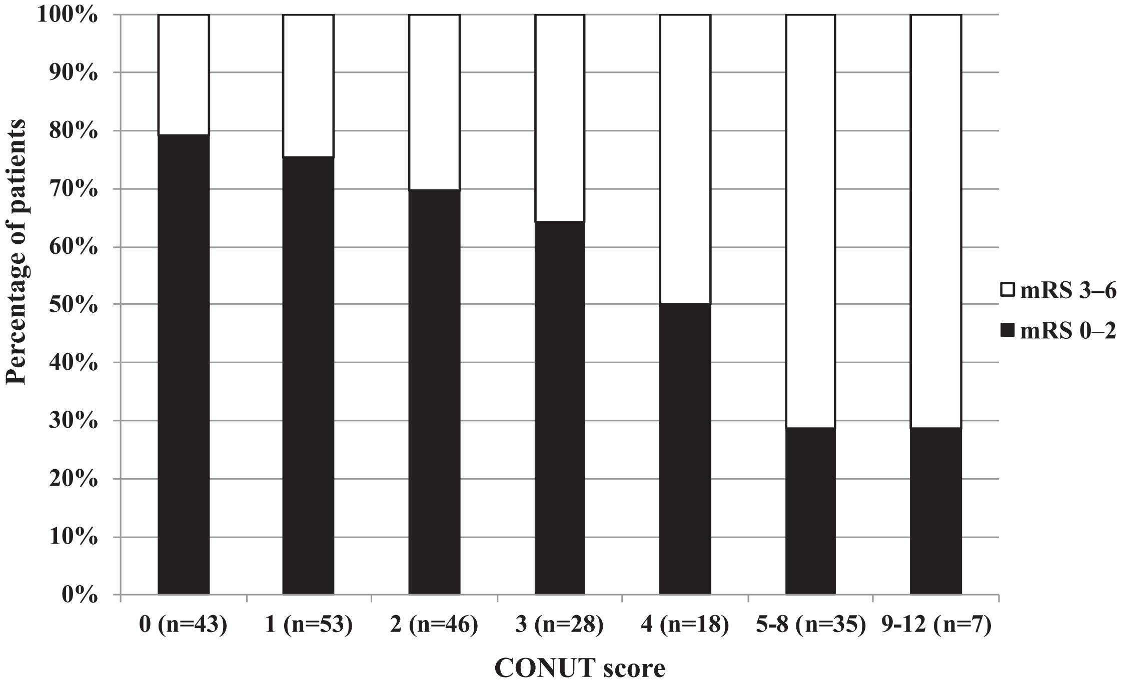
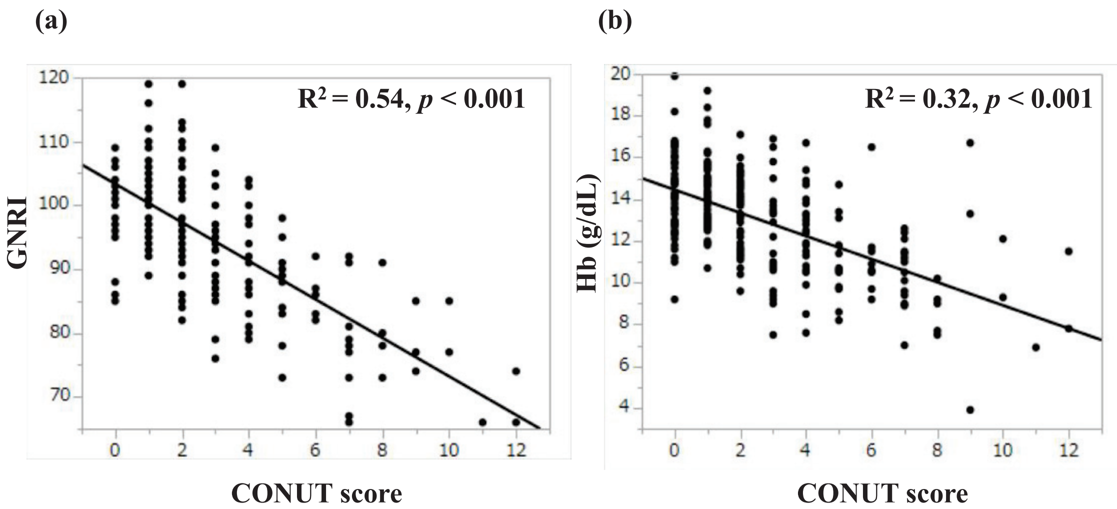

Patients with acute ischemic stroke admitted within 7 days of onset (n = 311)
excluded
・Pre-morbid mRS score ≥ 3 (n = 25)
・Lack of data required to calculate the CONUT score (n = 22)
Enrolled patients (n = 264)
excluded
・Lack of data on the functional outcomes 3 months after stroke onset (n = 34)
Main analyses performed for assessing the association between the functional outcomes and the CONUT score (n = 230)

Fig.2



100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of patients
0 (n=43)
1 (n=53)
2 (n=46)
3 (n=28)
4 (n=18)
5-8 (n=35)
9-12 (n=7)
CONUT score
mRS 3–6
mRS 0–2

Fig.3



(a)
$R^2 = 0.54$, $p < 0.001$
GNRI
120
110
100
90
80
70
0
2
4
6
8
10
12
CONUT score
(b)
$R^2 = 0.32$, $p < 0.001$
Hb (g/dL)
20
18
16
14
12
10
8
6
4
0
2
4
6
8
10
12
CONUT score

Table 1. Baseline characteristics at admission, and univariate analysis to determine the factors associated with 3-month functional outcome

	n = 264	mRS 0–2 (n = 145)	mRS 3–6 (n = 85)	*p*
Age (years)	70.9 ± 12.2	68.7 ± 11.8	74.7 ± 11.5	< 0.001
Female	93 (35.2)	41 (28.3)	34 (40.0)	0.067
Body mass index, kg/m^2	22.8 ± 4.0 (n = 262)	23.4 ± 4.3	21.8 ± 3.6 (n = 84)	0.005
Hypertension	197 (74.6)	112 (77.2)	59 (69.4)	0.189
Diabetes mellitus	92 (35.0) (n = 263)	51 (35.2)	32 (38.1) (n = 84)	0.658
Dyslipidemia	148 (56.3) (n = 263)	91 (62.8)	40 (47.6) (n = 84)	0.026
Daily alcohol intake	78 (32.2) (n = 242)	48 (35.0) (n = 137)	21 (27.6) (n = 76)	0.269
Current smoking	48 (20.0) (n = 241)	36 (26.1) (n = 138)	5 (6.8) (n = 74)	< 0.001
Atrial fibrillation	72 (27.4) (n = 263)	28 (19.3)	33 (39.3) (n = 84)	0.001
Chronic heart failure	50 (19.0)	20 (13.8)	21 (24.7)	0.037
Previous stroke	55 (20.8)	35 (24.1)	13 (15.3)	0.111
Previous ischemic heart disease	37 (14.0)	20 (13.8)	13 (15.3)	0.754
NIHSS score at admission	4 (1-11)	2 (1-4)	15 (4-24)	< 0.001
Thrombolysis	23 (8.7)	9 (6.2)	9 (10.6)	0.232
Stroke subtype				0.010
Small-vessel occlusion	37 (14.0)	27 (18.6)	6 (7.1)	

Large-artery atherosclerosis	47 (17.8)	31 (21.4)	10 (11.8)	
Cardioembolic stroke	87 (33.0)	44 (30.3)	31 (36.5)	
Other etiology	55 (20.8)	23 (15.9)	25 (29.4)	
Undetermined etiology	38 (14.4)	20 (13.8)	13 (15.3)	
Laboratory findings				
Albumin, g/dL	3.8 ± 0.6	3.9 ± 0.6	3.5 ± 0.6	< 0.001
Total cholesterol, mg/dL	188 ± 45	194 ± 41	178 ± 50	0.007
White blood cell, count/mL	7618 ± 3186	7307 ± 3113	8069 ± 3491	0.088
Lymphocyte count, count/mL	1485 ± 676	1590 ± 670	1290 ± 656	0.001
Hemoglobin, g/dL	13.0 ± 2.4	13.4 ± 2.4	12.3 ± 2.3	0.002
Nutritional indicators				
CONUT score	2 (1-4)	1 (1-3)	3 (1-6)	< 0.001
CONUT score of 5–12	48 (18.2)	12 (8.3)	30 (35.3)	< 0.001
GNRI	98 (89–103) (n = 262)	100 (94–104)	92 (83-100) (n = 84)	< 0.001
low GNRI (< 92)	82 (31.3) (n = 262)	30 (20.7)	39 (46.4) (n = 84)	< 0.001
anemia	104 (39.4)	49 (33.8)	43 (50.6)	0.012

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; CONUT, Controlling Nutritional Status; GNRI, Geriatric Nutritional Risk Index

Data are presented as the means ± SD for age, body mass index, each laboratory finding; as median (interquartile range) for baseline NIHSS score, CONUT score, and GNRI; and as number of patients (%) for others.

Table 2. Scoring system for the CONUT score [14]

Parameter	None	Light	Moderate	Severe
Serum albumin (g/dL)	≥ 3.50	3.00–3.49	2.50–2.99	< 2.50
Score	0	2	4	6
Total lymphocyte count (/mm^3)	≥ 1600	1200–1599	800–1199	< 800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥ 180	140–179	100–139	< 100
Score	0	1	2	3

Abbreviations: CONUT, Controlling Nutritional Status

Table 3. Indicators associated with poor outcome at 3 months

Indicators	Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*
CONUT score of 5–12	6.05 (2.95–13.09)	< 0.001	4.15 (1.52–11.67)	0.005
low GNRI (< 92)	3.32 (1.85–6.02)	< 0.001	2.29 (0.95–5.57)	0.065
anemia	2.01 (1.16–3.48)	0.012	1.99 (0.89–4.54)	0.092

Abbreviations: OR, odds ratio; CI, confidence interval; CONUT, Controlling Nutritional Status

Model 1: Univariate logistic analyses were performed to identify the indicators (CONUT score of 5–12, low GNRI, and anemia). Model 2: The factors listed in Table 2, except for laboratory findings and stroke subtypes, were selected for poor stroke outcome using a backward selection procedure, with a p value > 0.10 as the exclusion criterion for the likelihood ratio test. Next, multivariate logistic analysis was performed for each nutritional indicator (CONUT score, low GRNI, and anemia) and other baseline factors that remained as predictors of poor stroke outcome after the above-mentioned stepwise procedure.