Title 論文題目	Individualized nutritional treatment for acute stroke patients with malnutrition risk improves functional independence measurement: a randomized controlled trial (低栄養リスクを有する急性期脳卒中患者に対する個別栄養管理は機能的自立度を改善する:ランダム化比較試験)
Author(s) 著者	大槻, 郁人
Degree number 学位記番号	甲第3101号
Degree name 学位の種別	博士(医学)
Issue Date 学位取得年月日	2020-09-30
Original Article 原著論文	Geriatr Gerontol Int. 2020 Mar;20(3):176-182
Doc URL	
DOI	10.1111/ggi.13854
Resource Version	Author Edition

Individualized nutritional treatment for acute stroke patients with malnutrition risk improves functional independence measurement: a randomized controlled trial

Journal:	*Geriatrics & Gerontology International*
Manuscript ID	GGI-0750-2019.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Otsuki, Ikuto; Otaru General University, Anesthesia; Himuro, Nobuaki; Sapporo Medical University School of Medicine, Department of Public Health Tatsumi, Hiroomi; Sapporo Medical University School of Medicine, Department of Intensive Care Medicine Mori, Mitsuru; Hokkaido Chitose Rehabilitation University, Niiya, Yoshimasa; Otaru General Hospital, Department of Neurosurgery Kumeta, Yukihiro; Otaru General Hospital, Department of Anesthesia Yamakage, Michiaki; Sapporo Medical University School of Medicine, Department of Anesthesiology
Keywords:	Cerebrovascular disease < Geriatric Medicine < Clinical Medicine, Metabolism, Clinical Nutrision < Geriatric Medicine < Clinical Medicine, Rehabilitation Medicine / Physical Therapy < Clinical Medicine
Optional Keywords:	functional independence measurement, malnutrition, randomized controlled trial, nutritional treatment, stroke

Title Page

Individualized nutritional treatment for acute stroke patients with malnutrition risk improves functional independence measurement: a randomized controlled trial

Ikuto Otsuki[a], Nobuaki Himuro[b], Hiroomi Tatsumi[c], Mitsuru Mori[d], Yoshimasa Niiya[e], Yukihiro Kumeta[f], Michiaki Yamakage[g]

[a] Department of Anesthesia, Otaru General Hospital, 1-1-1 Wakamatsu, Otaru, Hokkaido 047-8550, Japan

[b] Department of Public Health, Sapporo Medical University School of Medicine, South 1, West 17, Chuo-ku, Sapporo, Hokkaido 060-8556, Japan

[c] Department of Intensive Care Medicine, Sapporo Medical University School of Medicine, South 1, West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan

[d] Department of Health Science, Hokkaido Chitose College of Rehabilitation, Satomi 2-10, Chitose, Hokkaido 066-0055, Japan

[e] Department of Neurosurgery, Otaru General Hospital, 1-1-1 Wakamatsu, Otaru, Hokkaido 047-8550, Japan

[f] Department of Anesthesia, Otaru General Hospital, 1-1-1 Wakamatsu, Otaru, Hokkaido 047-8550, Japan

[g] Department of Anesthesiology, Sapporo Medical University School of Medicine, South 1, West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan

Author Contributions

Ikuto Otsuki conceptualized the study and participated in the methodology, formal analysis, investigation, data curation, and writing of the original draft. Nobuaki Himuro participated in the formal analysis and manuscript review and editing. Hiroomi Tatsumi and Mitsuru Mori participated in the project administration. Yoshimasa Niiya and Yukihiro Kumeta participated in the manuscript review and editing. Michiaki Yamakage supervised the project.

Corresponding author:

Ikuto Otsuki

E-mail: mirrorname@hotmail.com

Tel: +81-134-25-1211; Fax: +81-134-32-6424

Address: Department of Anesthesia, Otaru General Hospital, 1-1-1 Wakamatsu, Otaru, Hokkaido 047-8550, Japan

*Current telephone number and address

Tel: +81-11-611-2111; Fax: +81-11-621-8059

Department of Anesthesiology, Sapporo Medical University School of Medicine

South 1, West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan

Running title: Nutritional support for stroke patients

Abstract

Aim

The aim of the present study was to investigate the effects of individualized nutritional treatment on the activities of daily living of acute stroke patients.

Methods

This was a randomized controlled study. The eligibility criteria were acute stroke, age over 65 years, and presence of malnutrition risk. Between September 2016 and December 2017, 128 patients were assigned to either the standard or intensive group (individualized nutritional treatment). The intensive group received energy that was calculated using the Harris–Benedict equation. The main outcome measures were the total functional independence measurement gain from the time of assignment to the time of discharge from the recovery hospital or at 3 months after the stroke onset and motor and cognitive functional independence measurement gains.

Results

Compared with the standard group, the intensive group had significantly higher median energy intake ($P < 0.001$); significantly greater functional independence measurement gains in the total score (42 vs. 22; $P = 0.02$) and motor subscore ($P = 0.01$) but similar cognitive subscore.

Conclusion

Individualized nutritional treatment improved the activities of daily living of elderly acute stroke patients with malnutrition risk.

UMIN number: UMIN000023954; Website: www.umin.ac.jp

Key words

functional independence measurement, malnutrition, nutritional treatment, randomized controlled trial, stroke

Introduction

Stroke is one of the leading causes of disability and mortality.[1] The main goals for acute stroke treatment and rehabilitation are to reduce mortality and disabilities and to increase independency in the activities of daily living (ADL).[2] In stroke patients, malnutrition is a common problem that has been associated with poor outcome[3,4]; increase in the number of cardiovascular events, infections,[5] and hospitalization days and cost[3]; and poor improvement in ADLs.[6] Stroke patients may be malnourished due to dysphagia, reduced level of consciousness, and cognitive dysfunction.[7,8] Moreover, stroke patients were reported to lose weight,[9] and the most significant factor associated with the changes in body weight was the amount of food intake.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline for neurology[7] recommended that all stroke patients be screened for malnutrition risk using the Malnutrition Universal Screening Tool (MUST).[7] Previous studies reported that the MUST can be used to predict the risk for negative outcomes and help patients benefit from nutrition therapy.[3,7] Although nutritional supplementation has been shown to improve nutritional status,[10] it did not improve the outcomes of the acute stroke patients in the large-scale FOOD trial.[11] However, the results did not account for the subgroup that was undernourished or had malnutrition risk.

Ha et al. reported that an individualized nutritional treatment strategy improved the quality of life of elderly acute stroke patients with malnutrition risk.[12] Rabadi et al. reported that intensive nutritional supplementation improved the motor recovery of stroke patients with malnutrition.[13] In a retrospective study, Kokura et al. reported that energy intake affected the improvements in the ADL of elderly stroke patients.[14] These reports implied

the importance of intensive nutritional support for acute stroke patients with malnutrition risk. On the other hand, Pellicane et al. reported that improvement in the ADL was not associated with energy intake.[15]

The mechanisms of neurologic recovery after stroke comprise local processes (early recovery) and central nervous system reorganization (later recovery). Early recovery includes resolution of poststroke edema, reperfusion of the ischemic penumbra, and resolution of diaschisis in the first few weeks.[16] We hypothesized that early nutritional intervention can prevent malnutrition and limb atrophy and contribute to the improvement of ADL after early neurologic recovery. Currently, there is no consensus on whether early individualized nutritional treatment can improve the ADL of acute stroke patients with malnutrition risk. This study investigated the relationship between individualized nutritional treatment and improvement in the ADL.

Methods

Design and setting

This was a prospective randomized single-blinded study that was conducted at Otaru General Hospital Japan between September 2016 and December 2017. The study protocol was approved by the Otaru General Hospital ethics committee and was registered with UMIN. Written informed consent was obtained after explaining this study to the patients or their families or guardian. The study procedures were performed according to the ethical recommendations in the Declaration of Helsinki.

Participants

We consecutively screened patients who were admitted to the neurosurgical and neurology wards of Otaru General Hospital. The eligibility criteria included stroke (i.e., cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage) and age over 65 years. In addition to the clinical findings, computed tomography scan or magnetic resonance imaging was performed on all patients for stroke diagnosis. Stroke severity was assessed based on the National Institutes of Health Stroke Scale (NIHSS). The patients excluded from the study were those who were critically ill and difficult to save; had severe dementia; were at the terminal stage of other diseases, such as cancer; had coexisting disease that required strict management; had liver cirrhosis; received albumin preparation; and were judged by the attending physician to be unsuitable for the study.

Nutritional screening was performed using the MUST[17] and blood tests on the 7th hospital day. The MUST comprised 5 grades and involved assessment of body mass index (BMI), percentage of weight loss, and effect of acute illness on dietary intake. Based on the previously reported association between relatively low serum albumin level and poor outcomes in patients with stroke,[18,19] the present study enrolled patients with high risk for malnutrition, which was defined as a MUST score of ≥2 or serum albumin of ≤3.0 g/dL.

Sample size

This study accrued 64 patients in each arm. The objective of the enrollment was based on a published study,[13] and sample size was calculated using the Power and Sample Size Calculation software (version 3.1, Department of Biostatistics, Vanderbilt University, Nashville, TN, USA).[20] After choosing “t-test”, “sample size”, “independent”, two-sided $\alpha = 0.05$, power = 0.8, and $\delta = 8$ to detect differences between 2 groups; $\sigma = 13$ as the

standard deviation (SD) of the outcome; and m = 1 as the ratio of the number of samples, the number of patients in each arm was calculated as 42. The δ and σ were based on the functional independence measurement (FIM) gain that was described in a published study.[13] In consideration of dropouts, the number of patients in each arm was increased by about 50%.

Randomization

Eligible patients were randomized to either the standard group or the intensive group (individualized nutritional treatment) in a 1:1 ratio. We adopted the block random allocation method, with 1 block comprising 8 people. The sequence of treatment allocation was prepared from a computer-generated randomization list,[21] which was managed by individuals who were not involved in the study. We obtained the allocation number by reporting eligible patients to the administrators. Eligibility assessment was performed by those involved in the study, whereas assignment was performed by those not related to the study.

Statistical methods

All the available data for the primary and secondary outcomes were used for the analysis. Categorical variables were presented as numbers and percentages, whereas continuous and ordinal variables were presented as median (interquartile range). The statistical significance of intergroup differences was assessed using the chi-square test for categorical variables and the Mann–Whitney *U*-test for continuous and ordinal variables. To adjust for the possible effect of missing data on the study results, the mean changes in

the total FIM score were analyzed using restricted maximum likelihood estimation for linear mixed effect models under "missing at random" assumptions. In all analyses, $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the software package SPSS (version 23, IBM Corporation, Tokyo, Japan)

Intervention

At Otaru General Hospital, the general menu of the selected meals for hospitalized patients, including those admitted for stroke, was chosen and preadjusted according to the general physique of the Japanese and was available at 1000, 1200, 1400, 1600, 1800, and 2000 kcal per day. The applicable meal was chosen from the preadjusted menu, so that each patient in the standard group was provided the daily caloric requirement, which was calculated as body weight (kg) × 25 kcal, according to the stroke department's protocol. If there was no menu that provided the required daily caloric intake, the standard group was provided a meal in the 25–30 kcal/kg range.

For the intensive group, the daily caloric requirement was calculated by dietitians using the Harris–Benedict equation and according to the progress of patient rehabilitation; the stress coefficient ranged from 1.1 to 1.4 and the activity coefficient ranged from 1.0 to 1.4. Based on the calculated caloric requirement, the meals provided for all patients in the intensive group were taken orally or by enteral tube feeding; the latter was used for patients who had severe dysphagia and anorexia. We did not prescribe parenteral nutrition for this study because stroke patients may require strict management of their water intake and output.

At our hospital, the amount of protein was predetermined in the preadjusted menu.

Therefore, in this study population, the amount of protein was determined in conjunction with and was directly proportional to the amount of calories provided. Daily intake of energy and protein was calculated by multiplying the ratio of the actual food intake by the provided calories and proteins in the meal, respectively. In each group, the amount of actually ingested meal was recorded by the nurses. The nurses were trained to ensure consistency in determining food intake. We calculated the average values of the energy provided and energy intake from the time of assignment until transfer to a recovery hospital. Nutritional treatment was administered until the patient was discharged from our hospital, and no nutritional intervention was done at the recovery hospital. For each group, the usual stroke treatment and rehabilitation were done. The dietitians, nurses, and physical therapists of our hospital were not blinded in their calculation and provision of meals, but the patients and primary outcome assessors were blinded.

Outcome measures

The primary outcome variable was total FIM gain from the time of assignment to the time of discharge from the recovery hospital. If the patient was not discharged from the recovery hospital at 3 months after the stroke onset, FIM was measured at that time. FIM is one of the most common tools to measure ADL performance.[22] The total FIM score ranged from 18 to 126 points, and a lower score indicated poor performance of ADL. The secondary outcome variables included motor and cognitive FIM gains and physical measurements (i.e., body weight, arm circumference, thigh circumference, and calf circumference).

To ensure accuracy, all FIM scoring and physical measurements were conducted by

physical therapists. In addition, we made a guidebook with pictures of the physical measurement method, in order to reduce measurement error. The physical measurement method is shown in Table S1. Because the measuring machines can differ among hospitals, physical measurements were carried out at our hospital before transfer and at the recovery hospital upon admission. The estimated values were calculated using the difference between admission and discharge at the recovery hospital.

Results

Participant inclusion

We screened 1,318 patients during the registration period, and 128 acute stroke patients with malnutrition risk over the age of 65 years were randomly assigned to either the standard or intensive group (Fig. 1). The reasons for drop out cases were withdrawal of consent (n = 4), development of another disease (n = 8), absence of reply from the recovery hospitals (n = 8), and discharge to home without transfer to a recovery hospital (n = 14).

Diabetes patients whose blood glucose level could not be controlled despite use of the insulin sliding scale by the 7th hospital day were excluded due to “coexisting disease that required strict management”.

Baseline characteristics

The baseline characteristics of acute stroke patients with malnutrition risk and over the age of 65 years are shown in Table 1. The 2 groups had no significant differences in age, sex, weight, height, BMI, stroke type, NIHSS, total FIM score, motor FIM subscore, cognitive FIM subscore, and laboratory data.

Energy and protein provided/intake

The amount of energy provided and intake were significantly higher in the intensive group than in the standard group (Table 2).

Rehabilitation time and length of stay in our hospital

The average rehabilitation time by physical therapists and length of stay before transfer were similar between the 2 groups (Table 2).

Body weight and physical measurement

There was no significant difference in the body weight between the 2 groups (Table 3). In general, the circumferential measurements were smaller in the standard group than in the intensive group (Table 3). Thigh circumference was significantly different between the 2 groups.

FIM gain

Data on the primary outcome were available and obtained in 94 patients (Table 3). The total FIM gain improved significantly in the intensive group compared to the standard group (42 vs. 22; P = 0.02), and thus was mainly due to improvements in the motor FIM subscore (standard group, 17 vs. intensive group, 35; P = 0.01). The cognitive FIM gain was not significantly different between the standard and intensive groups (3 vs. 7, respectively; P = 0.10).

Exploratory analysis was performed by classifying malnutrition risk only by MUST

(Table S2). The results did not change significantly.

The linear mixed effect model, which used age, sex, NIHSS, and body weight to evaluate the total FIM score, showed an interaction between the group and period from assignment to discharge (P = 0.02) (Fig. 2).

Discussion

The present study had important clinical findings. In particular, individualized nutritional treatment of elderly acute stroke patients with malnutrition risk improved the ADL. The percentage of malnourished stroke patients was reported to range from 6.1% to 62%.[23] One of the goals of acute stroke rehabilitation is to increase independency in ADL.[2] The combination of rehabilitation and nutrition was shown to improve the functional prognosis of acute stroke patients.[24,25] Two randomized controlled studies reported that intake of more energy improved the outcome of acute stroke patients with malnutrition risk. Ha et al. reported that individualized nutritional treatment can improve the quality of life[12]; the differences in daily energy intake between the study groups were similar (i.e., 4 kcal/kg in our study and 3.6 kcal/kg in the previous study). Rabadi et al.[13] compared 2 supplements that were added every 8 hours to ordinary hospital meals; the nutritional supplement was higher in the intensive group (240 calories, 11 g of protein) than in the standard group (127 calories, 5 g of protein). Similar to their study, our present study showed that the total FIM gain and motor FIM gain in the intensive group increased, but the cognitive FIM gain did not significantly differ from that in the standard group.

Compared with the minimal clinically important differences (MCID),[26] the total FIM gain was lower but the motor and cognitive FIM gains were higher in this study (this

study vs. MCID: total, 20 vs. 22; motor, 18 vs. 17; cognitive, 4 vs. 3). This study supports that nutritional intervention improves ADL clinically.

The Academy of Nutrition and Dietetic and the American Society for Parenteral and Enteral Nutrition declared that weight loss and loss of muscle or fat mass were important characteristics of malnutrition.[27] Using physical measurements, Zheng et al. showed the importance of nutritional treatment for acute stroke patients who received either enteral nutrition (about 20–30 kcal/kg/day) or family-managed nutrition.[28] Compared with the family-managed nutrition group, the nutritional treatment group had less decrease in the triceps skinfold thickness and arm muscle circumference on the nonparalyzed side. The present study showed that the decrease in arm circumference on the nonparalyzed side was 4.5% in the standard group and only 1.4% in the intensive group and that the circumference was generally smaller in the standard group than in the intensive group on both the paralyzed and nonparalyzed sides. A previous study indicated that muscle thickness reduction due to aging was greater in the thigh compared with the arm and calf.[29] Our study showed that the reduction rate in thigh circumference was greater. Although changes in muscle thickness due to aging may not be by the same mechanism as reduced activity due to post-stroke effects or malnutrition, our study results were similar to the previous study. Malnutrition reduces the effectiveness of rehabilitation because of impaired muscle function.[30] The present study implied that maintenance of nutritional status might prevent muscle atrophy and lead to improvements in motor FIM gain.

The ESPEN guidelines for neurology[7] recommended screening of the nutritional status of all stroke patients within 48 hours of admission, in order to detect the risk for malnutrition by methods, such as the MUST. In the present study, nutritional screening and

treatment were started on the 7th hospital day. The results of the linear mixed effect model implied that early intervention may lead to more improvements in the ADL. Preventing malnutrition with early nutritional intervention is important to increase the efficiency of rehabilitation after early neurologic recovery.

The present study had some limitations. First, we used albumin level as an eligibility criterion. However, recently albumin level has been shown to not specifically indicate malnutrition in the acute phase.[27] An exploratory analysis was performed by classifying malnutrition risk only by MUST. The results did not change significantly, because most patients had a MUST score of ≥2 and only four patients had a MUST score of <2 and serum albumin of ≤3.0 g/dL. Second, the single-center and single-blinded design might have limited the generalizability of the results. Third, there was a possibility of measurement error because of the differences in personnel and measuring equipment between our hospital and the recovery hospital. Fourth, actual energy intake was calculated based on visual observation by nurses. Fifth, we examined patients with stoke in this study without considering the severity or type of stroke. Further study is needed to investigate in detail the patients who may benefit from individualized nutritional treatment, according to patient and/or disease characteristics, such as stroke severity and type.

In conclusion, individualized nutritional treatment improved the ADL of acute stroke patients with malnutrition risk. The importance of nutritional management in the early stage of stroke is underscored.

Acknowledgements

We would like to thank Y. Wada (dietitian), the neurosurgical ward nurses, and the

rehabilitation staff of Otaru General Hospital for their cooperation in this project. We received permission from those named in the acknowledgements.

Conflict of interest statement and funding sources

This study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors declare no conflict of interest.

References

1 Thrift AG, Thayabaranathan T, Howard G, et al. Global stroke statistics. Int J Stroke. 2017; 12: 13-32.

2 Kjellstrom T, Norrving B, Shatchkute A. Helsingborg Declaration 2006 on European stroke strategies. Cerebrovasc Dis. 2007; 23: 231-41.

3 Gomes F, Emery PW, Weekes CE. Risk of Malnutrition Is an Independent Predictor of Mortality, Length of Hospital Stay, and Hospitalization Costs in Stroke Patients. J Stroke Cerebrovasc Dis. 2016; 25: 799-806.

4 Collaboration FT. Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. Stroke. 2003; 34: 1450-6.

5 Maruyama K, Nakagawa N, Koyama S, Maruyama JI, Hasebe N. Malnutrition Increases the Incidence of Death, Cardiovascular Events, and Infections in Patients with Stroke after Rehabilitation. J Stroke Cerebrovasc Dis. 2018; 27: 716-23.

6 Nishioka S, Wakabayashi H, Nishioka E, Yoshida T, Mori N, Watanabe R. 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. 2016; 116: 837-43.

7 Burgos R, Breton I, Cereda E, et al. ESPEN guideline clinical nutrition in neurology. Clin Nutr. 2018; 37: 354-96.

8 Chen N, Li Y, Fang J, Lu Q, He L. Risk factors for malnutrition in stroke patients: A meta-analysis. Clin Nutr. 2019; 38: 127-35.

9 Paquereau J, Allart E, Romon M, Rousseaux M. The long-term nutritional status in stroke patients and its predictive factors. J Stroke Cerebrovasc Dis. 2014; 23: 1628-33.

10 Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. JPEN J Parenter Enteral Nutr. 1998; 22: 315-9.

11 Dennis MS, Lewis SC, Warlow C, Collaboration FT. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. Lancet. 2005; 365: 755-63.

12 Ha L, Hauge T, Spenning AB, Iversen PO. 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. 2010; 29: 567-73.

13 Rabadi MH, Coar PL, Lukin M, Lesser M, Blass JP. Intensive nutritional supplements can improve outcomes in stroke rehabilitation. Neurology. 2008; 71: 1856-61.

14 Kokura Y, Wakabayashi H, Nishioka S, Maeda K. Nutritional intake is associated with activities of daily living and complications in older inpatients with stroke. Geriatr Gerontol Int. 2018; 18: 1334-9.

15 Pellicane AJ, Millis SR, Barker KD, et al. The effect of protein and calorie intake on prealbumin, complications, length of stay, and function in the acute rehabilitation inpatient with stroke. NeuroRehabilitation. 2013; 33: 367-76.

16 The Stroke Rehabilitation Clinician's Handbook, Canadian Partnership for Stroke Recovery (Accessed June 1, 2019, at http://www.ebrsr.com/clinician-handbook)

17 Stratton RJ, King CL, Stroud MA, Jackson AA, Elia M. 'Malnutrition Universal Screening Tool' predicts mortality and length of hospital stay in acutely ill elderly. Br J Nutr. 2006; 95: 325-30.

18 Dziedzic T, Slowik A, Szczudlik A. Serum albumin level as a predictor of ischemic stroke outcome. Stroke. 2004; 35: e156-8.

19 Babu MS, Kaul S, Dadheech S, Rajeshwar K, Jyothy A, Munshi A. Serum albumin levels in ischemic stroke and its subtypes: correlation with clinical outcome. Nutrition. 2013; 29: 872-5.

20 "Power and Sample Size Calculation" software version 3.1, Department of Biostatistics, Vanderbilt University. (Accessed May 1, 2016, at http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize)

21 Randomization.com. (Accessed May 4, 2016, at http://www.randomization.com/)

22 Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC. The reliability of the functional independence measure: a quantitative review. Arch Phys Med Rehabil. 1996; 77: 1226-32.

23 Foley NC, Salter KL, Robertson J, Teasell RW, Woodbury MG. Which reported estimate of the prevalence of malnutrition after stroke is valid? Stroke. 2009; 40: e66-74.

24 Kokura Y, Maeda K, Wakabayashi H, Nishioka S, Higashi S. 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. 2016; 25: 1335-41.

25 Nip WF, Perry L, McLaren S, Mackenzie A. Dietary intake, nutritional status and rehabilitation outcomes of stroke patients in hospital. J Hum Nutr Diet. 2011; 24: 460-9.

26 Beninato M, Gill-Body KM, Salles S, Stark PC, Black-Schaffer RM, Stein J. Determination of the minimal clinically important difference in the FIM instrument in patients with stroke. Arch Phys Med Rehabil. 2006; 87: 32-9.

27 White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and

Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012; 36: 275-83.

28 Zheng T, Zhu X, Liang H, Huang H, Yang J, Wang S. Impact of early enteral nutrition on short term prognosis after acute stroke. J Clin Neurosci. 2015; 22: 1473-6.

29 Masae M, Hiroaki K, Kazumi A, Shinya K, Tetsuo F. Site-related Differences in Muscle Loss with Aging. ”A Cross-sectional Survey On The Muscle Thickness in Japanese Men Aged 20 to 79 Years”. International Journal of Sport and Health Science. 2003; 1: 34-40.

30 Lopes J, Russell DM, Whitwell J, Jeejeebhoy KN. Skeletal muscle function in malnutrition. Am J Clin Nutr. 1982; 36: 602-10.

Figure legends

Figure 1. Flowchart of the selection of elderly acute stroke patients with malnutrition risk

MUST = Malnutrition Universal Screening Tool

Figure 2. Linear mixed effects model for the comparison of the mean total FIM score between the standard and individualized nutritional treatment groups

The total FIM score has interactions with the groups and period from assignment to discharge. FIM = functional independence measurement

Supporting information legends

Table S1. Physical measurement method

Table S2. Outcome measures upon discharge from the recovery hospital or 3 months after the stroke onset (exploratory data analysis: MUST ≥ 2).

Values are presented as median (25%–75% interquartile range). FIM = functional independence measurement, 95% CI = 95% confidence interval, MUST = Malnutrition Universal Screening Tool.

Table 1. Baseline characteristics of elderly acute stroke patients with malnutrition risk (N = 124)

Characteristics	Standard group (n = 62)	Intensive group (n = 62)	P value
Age (years)	80.5 (75-86)	78.5 (71-85)	0.32
Sex, M (%)	23 (37.1)	27 (43.5)	0.46
Body weight on assignment (kg)	51.2 (42.9-57.0)	54.2 (46.0-60.5)	0.07
Height on assignment (cm)	154 (144-162)	154 (148-163)	0.22
Body mass index (kg/m^2)	21.7 (18.8-23.8)	22.6 (19.5-25.0)	0.26
Stroke type, n (%)			0.77
Cerebral infarction	37 (59.7)	33 (53.2)	
Cerebral hemorrhage	19 (30.6)	22 (35.5)	
Subarachnoid hemorrhage	6 (9.7)	7 (11.3)	
Stroke severity			
NIHSS on admission	8 (3-20)	8.5 (3-16)	0.94
Assignment			
Total FIM score	41 (21-59)	43 (29-67)	0.40
Motor FIM subscore	19.5 (13-36)	23.5 (14-44)	0.43
Cognitive FIM subscore	17 (7-24)	17 (13-25)	0.59
Albumin (g/dL)	3.0 (2.8-3.4)	3.1 (2.8-3.3)	0.78

NIHSS = National Institutes of Health Stroke Scale, FIM = functional independence measurement

Values are presented as median (25%–75% interquartile range)

Table 2. Energy and protein provided and ingested and the rehabilitation time and length of stay before transfer in the study groups

	Standard group (n = 61)	Intensive group (n = 60)	P value
Provided energy (kcal/day)	1400 (1214-1435)	1669 (1500-1805)	<0.001
Energy intake (kcal/day)	1200 (1085-1297)	1496 (1200-1629)	<0.001
Energy intake (kcal/kg/day)	23.3 (20.3-27.0)	27.3 (23.2-32.1)	0.001
Provided protein (g/day)	57.3 (55.0-60.0)	66.6 (60.6-71.9)	<0.001
Protein intake (g/day)	49.6 (41.5-58.5)	59.7 (47.1-66.5)	0.001
Protein intake (g/kg/day)	1.0 (0.9-1.2)	1.1 (0.9-1.3)	0.05
Energy intake methods			0.66
Oral only, n (%)	41 (67.2)	44 (73.3)	
Enteral only, n (%)	12 (19.7)	11 (18.3)	
Oral and enteral, n (%)	8 (13.1)	5 (8.3)	
Rehabilitation (unit/day)†	2.5 (1.5-3.2)	2.6 (1.9-3.2)	0.44
Length of stay (days)	30 (21-41)	28 (21-39)	0.52

Values are presented as median (25%–75% interquartile range)

†one unit = 20 minutes

Table 3. Outcome measures upon discharge from the recovery hospital or 3 months after the stroke onset

	Standard group (n = 49)			Intensive group (n = 45)			P value for Difference and Δ%	R (Effect size)
	Assignment	Discharge	Difference (95% CI)	Assignment	Discharge	Difference (95% CI)		
Total FIM score	37 (20-56)	67 (42-106)	22 (21-33)	42 (26-62)	85 (57-113)	42 (31-45)	0.02	0.25
Motor FIM subscore	19 (13-34)	41 (27-75)	17 (17-28)	22 (13-42)	65 (39-83)	35 (26-37)	0.01	0.26
Cognitive FIM subscore	14 (7-25)	20 (10-31)	3 (3-6)	16 (11-21)	25 (18-31)	7 (5-9)	0.10	0.17
			Δ% (95% CI)			Δ% (95% CI)		
Body weight (kg)	52.0 (45.9-57.1)	49.8 (42.6-54.0)	-5.1 (-7.0 to -3.8)	55.3 (49.7-60.5)	52.3 (46.5-58.1)	-4.9 (-7.4 to -3.4)	0.57	0.06
Paralyzed side			Δ% (95% CI)			Δ% (95% CI)		
Arm circumference (cm)	25.4 (24.0-27.8)	24.7 (23.1-26.6)	-3.4 (-7.1 to -1.9)	26.2 (24.5-28.8)	25.9 (23.7-27.9)	-2.7 (-5.7-0.3)	0.33	0.12
Thigh circumference (cm)	38.9 (35.0-41.7)	37.6 (33.9-39.6)	-6.3 (-7.8 to -3.3)	40.0 (37.7-43.1)	39.5 (36.5-42.6)	-1.5 (-4.0-0.5)	0.02	0.28
Calf circumference (cm)	29.9 (28.4-31.6)	29.8 (27.3-30.7)	-5.0 (-6.7 to -2.1)	31.2 (29.4-33.2)	31.0 (29.3-32.7)	-2.3 (-4.5 to -0.3)	0.14	0.18
Nonparalyzed side								

Arm circumference (cm)	25.6 (24.1-28.0)	24.9 (23.0-26.7)	-4.5 (-6.3 to -2.1)	27.2 (23.4-28.5)	25.5 (23.8-28.9)	-1.4 (-4.2-0.3)	0.14	0.16
Thigh circumference (cm)	39.3 (35.6-42.9)	38.2 (34.7-41.4)	-2.7 (-6.6 to -2.2)	40.6 (37.5-43.6)	40.1 (37.7-43.0)	-1.1 (-3.0-0.9)	0.02	0.25
Calf circumference (cm)	30.2 (28.2-31.8)	29.6 (27.3-31.1)	-2.2 (-4.9 to -1.7)	31.2 (29.2-33.7)	30.5 (28.4-32.6)	-1.3 (-3.4-0.4)	0.14	0.16

FIM = functional independence measurement, 95% CI = 95% confidence interval

Values are presented as median (25%–75% interquartile range)

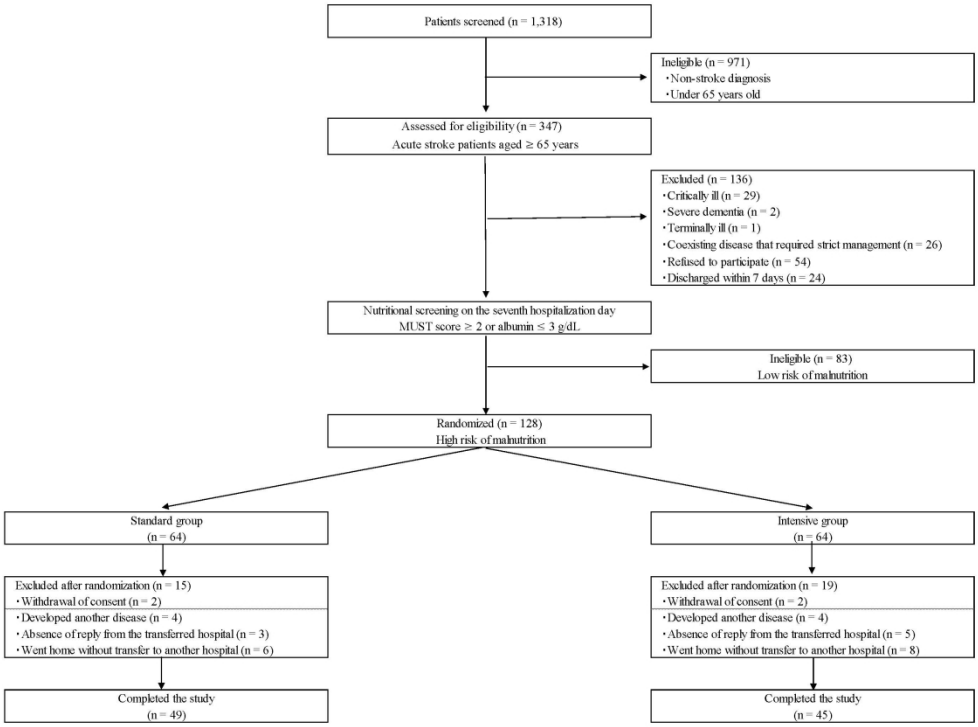

Figure 1. Flowchart of the selection of elderly acute stroke patients with malnutrition risk
MUST = Malnutrition Universal Screening Tool

355x266mm (200 x 200 DPI)

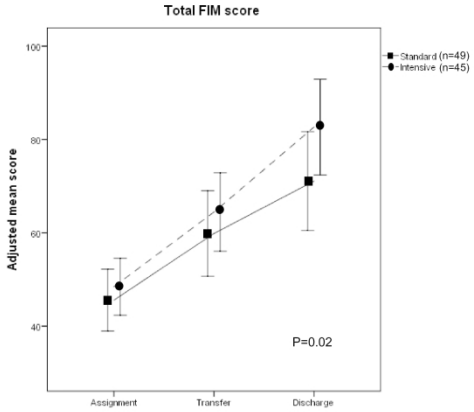

Figure 2. Linear mixed effects model for the comparison of the mean total FIM score between the standard and individualized nutritional treatment groups
The total FIM score has interactions with the groups and period from assignment to discharge.
FIM = functional independence measurement

355x266mm (300 x 300 DPI)