

## Original Article

# Impact of energy intake on the survival rate of patients with severely ill stroke

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**INTRODUCTION:** Stroke accounts for approximately 10% of all deaths. We examined whether energy intake influences the survival rate of severely ill stroke patients. **METHODS:** We analyzed 86 consecutive severely ill stroke patients. Patients' background was compared between survivors and non-survivors. Average energy intakes in seven different periods from day one to seven following neurosurgical care unit (NCU) admission were compared between two groups, to examine which period is proper to show an energy difference. Groups were stratified by average total energy intake (group E-I, -II, -III, and -IV;  $\leq 8.25$ , 8.25-16.5, 16.5-25, and  $>25$  kcal/kg/day, respectively), and cumulative survival rate for 90 days after NCU admission was analyzed. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to examine the effect of confounder factors. **RESULT:** Patients' background did not differ significantly between the two groups. Average daily energy intake for the first seven NCU days of non-survivors was significantly lower than that of survivors ( $p=0.034$ ). The survival rate of group E-II was significantly higher than that of group E-I, which was set as a reference ( $p=0.030$ ). The adjusted HR of E-II was also significantly lower than that of group E-I (HR=0.19,  $p=0.047$ ), although E-III did not show significance (HR=0.52,  $p=0.279$ ). **CONCLUSION:** Energy intake assessment should be conducted for at least seven days following NCU admission. An average total energy intake ranging from 8.25 to 16.5 kcal/kg/day and enteral feeding increases survival rate in severely ill stroke patients.

**Key Words:** stroke, outcome, energy intake, glasgow coma scale, neurosurgical care unit

## INTRODUCTION

Stroke has been identified as the second-leading cause of death worldwide by the World Health Organization<sup>1</sup> (10.8% mortality rate), and fourth-leading cause in Japan by the Japanese Ministry of Health, Labour and Welfare (9.9% mortality rate).<sup>2</sup> With one-tenth of deaths resulting from stroke, prevention and treatment is a critical issue. However, the association between outcome and energy intake in stroke patients has not been fully studied. Evidence from clinical studies of energy intake will contribute to improving the outcomes of critically ill stroke patients, but few such studies have appeared.

Nutritional support has been shown to reduce mortality rate,<sup>3</sup> shorten the length of hospital stay,<sup>4</sup> and improve quality of life and handgrip strength<sup>5</sup> in patients with stroke. However, the optimal energy intake required to achieve such clinical outcomes has not yet been identified. Guidelines of nutritional support for patients with stroke have been published in the United States,<sup>6</sup> Europe,<sup>7</sup> and Japan.<sup>8</sup> Although these guidelines cover the issues of dehydration, tube feeding, percutaneous endoscopic gastrostomy, dysphagia, and blood sugar control, the optimal energy intake required to reduce comorbidity and mortality has not been addressed.

In general, stroke patients with less severe neurological injury have lower mortality and can be discharged earlier without nutritional support. Here, therefore, we restricted entry into this study to stroke patients with severe neurological damage. In this context and from the aspect of nutritional support, we hypothesized that the identification of optimal energy intake of stroke patients with severe neurological damage could improve survival rate.

## METHODS

### Subjects

This study was conducted under a retrospective observational chart review design. The enrolled patients consisted of consecutive admissions to the Neurosurgical Care Unit

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(NCU) in a single neurosurgical institution over more than two days between May 2008 and February 2010 with diagnoses of cerebral infarction or cerebral hemorrhage ( $n=160$ ). Patients who were admitted to the NCU for more than two days were recruited, non-survivors during two days after NCU admission were excluded. Other exclusion criteria included 1) no weight data ( $n=12$ ); 2) no Glasgow Coma Scale (GCS) score ( $n=6$ ); 3) less-critically ill patients<sup>9</sup> with a GCS score  $>13$  ( $n=51$ ); and 4) lost to follow-up ( $n=5$ ). The remaining 86 patients were included in the further analyses.

The study was approved by the Research Ethics Committee of the institution.

### Collected data

Demographics, anthropometrics, laboratory data, level of consciousness, severity of general condition, and actual daily energy intake were collected from the medical records of subjects. These data were collected at NCU admission day, except for actual daily energy intake. Demographic data included age; gender; cause of stroke, cerebral infarction or cerebral hemorrhage; and comorbidities such as hypertension, diabetes, dyslipidemia, thyroid diseases, congestive heart disease, and liver disease. Anthropometric data included height, body weight, and body mass index (BMI). Laboratory data consisted of hemoglobin (Hb), serum albumin (Alb), and C-reactive protein (CRP). Level of consciousness and severity of general condition were assessed by the GCS score<sup>10</sup> and Sequential Organ Failure Assessment (SOFA) score,<sup>11,12</sup> respectively. Actual daily energy intakes (kcal/kg actual body weight) were collected on a daily basis during the first week of NCU admission. Nutritional routes, enteral or parenteral, were also assessed.

### Outcomes

Outcomes were mortality rate at 90 days after NCU admission and cumulative survival rate for 90 days after NCU admission.

To analyze clinical outcome, subjects who were discharged in remission from the hospital earlier than day 90 and for whom no further information was available were considered as survivors, and subjects who died within 90 days were considered as non-survivors.

### Comparison of background between survivors and non-survivors

Background characteristics of survivors and non-survivors were compared to determine whether they influenced clinical outcomes.

### Comparison of average energy intakes between survivors and non-survivors

The cumulative energy intake for total, enteral and parenteral administrations during the first week of NCU admission was compared. When a significant difference in cumulative energy intake was identified, average daily energy intake was calculated in seven different periods from days one to seven after NCU admission. After that, average daily energy intake of seven different periods was compared, to examine the period with a different average energy intake between survivors and non-survivors.

### Impact of energy intake on cumulative survival rate

Subjects were divided into four groups according to daily average total energy intake (kcal/kg/day):  $\leq 8.25$  (group E-I),  $8.25 < \leq 16.5$  (group E-II),  $16.5 < \leq 25$  (group E-III), and  $> 25$  (group E-IV), respectively. In this analysis, 8.25 kcal/kg/day, which is one-third of the recommended value for healthy adults (25 kcal/kg/day),<sup>13</sup> was considered as one unit of energy intake.

Cumulative survival rates for 90 days after NCU admission were compared among groups stratified by average total energy intake. Moreover, crude hazard ratios (HRs) and 95% confidence intervals (CIs) and HRs after adjustment for confounding factors of age, CRP levels, and SOFA scores, were calculated.

### Association with survival rate and nutritional route

To analyze the influence of route on cumulative survival rate, energy intake through the enteral and parenteral routes was individually compared among the four groups classified to analyze HRs in the previous analysis.

### Statistical analysis

Differences between two groups were determined using the Mann-Whitney's *U* test. To determine the differences between three or more groups, data were analyzed by the Kruskal-Wallis test, followed by the Steel-Dwass test. Survival analysis was assessed using the Kaplan-Meier survival curve and log rank test. Cox regression analysis was used to calculate HRs and 95% CIs. Data were expressed as median (25<sup>th</sup> and 75<sup>th</sup> percentiles) or HR (95% CI). Differences in two-tailed *p* values  $< 0.05$  were considered statistically significant for all analyses. Statistical analysis was performed using the statistical package PASW 18.0 for Windows (SPSS Inc, Chicago, IL, USA) and Ekuseru-Toukei 2010 (Social Survey Research Information Co, Ltd, Tokyo, Japan).

## RESULTS

Patients' characteristics are described in Table 1.

### Comparison of background between survivors and non-survivors

Background characteristics of survivors and non-survivors did not differ significantly (Table 2).

### Comparison of average energy intakes between survivors and non-survivors

The cumulative energy intake, total and enterally administered, of survivors was significantly higher than those of non-survivors (Table 2). The average total energy intakes calculated on a daily basis during the first seven days of NCU admission of the non-survivor group were significantly lower than that of survivors (10.8 (6.5, 16.1) vs 7.1 (4.0, 11.0),  $p=0.034$ , Figure 1), whereas the other average energy intake amounts calculated for different periods were not significantly different between the two groups. These results suggest that at least seven days is required to observe a significant difference in energy intake between groups classified by their living status. In other words, the first seven days following NCU admission might be considered the optimal period in which to assess energy intake to distinguish living status.

**Impact of energy intake on cumulative survival rate**

When classifying patients by average actual energy intake for first seven NCU days, cumulative survival rate during 90 days in group E-II was significantly higher than that in group E-I ( $p=0.030$ , Figure 2). In this analysis, group E-IV (25 kcal/kg/day $<$ ) was excluded due to the low number of patients ( $n=2$ ).

The HR of mortality for 90 days among these groups was also calculated to determine the intensity of energy impact among the different groups. The crude HRs of groups E-II and E-III did not differ significantly when reference was set at group E-I (Table 3). In contrast, only the adjusted HR of E-II showed a significant difference

(HR=0.19, 95% CI=0.04-0.97,  $p=0.047$ , Table 3).

SOFA score did not differ significantly among groups classified by average energy intake (group E-I vs E-II vs E-III = 5.0 (3.0, 8.0) vs 5.0 (4.0, 6.0) vs 2.5 (1.8, 6.5),  $p=0.473$ ).

**Association with survival rate and nutritional route**

Because the first seven days was necessary to observe a difference in energy intake in the survivor and non-survivor groups, average energy intake for the first seven days was used in this analysis. The result was that enteral energy intake showed a significant difference, although parenteral energy intake did not differ significantly (Fig-

**Table 1.** Patients characteristics

Characteristics	All subjects n = 86	Cerebral infarction n = 33	Cerebral hemorrhage n = 53	$p^\dagger$
<b>Demographics</b>				
Age, y	76.0 (64.0, 83.0)	80.0 (75.5, 89.0)	70.0 (58.5, 81.0)	<0.001
Gender				0.773
Men, % (n)	53 (46)	52 (17)	55 (29)	
Women, % (n)	47 (40)	48 (16)	45 (24)	
<b>Anthropometry</b>				
Height, cm	158 (150, 165)	158 (150, 164)	156 (150, 165)	0.656
Weight, kg	55.0 (45.0, 65.0)	52.0 (46.5, 60.0)	55.0 (44.5, 66.0)	0.418
Body mass index, kg/m <sup>2</sup>	21.9 (19.8, 24.4)	21.4 (20.0, 23.1)	22.0 (19.3, 25.0)	0.675
<b>Laboratory data</b>				
Hemoglobin, g/dL	13.1 (12.3, 14.5)	12.7 (12.2, 13.9)	13.3 (12.3, 15.3)	0.118
Serum albumin, g/dL	4.0 (3.8, 4.3)	3.9 (3.4, 4.2)	4.1 (3.9, 4.3)	0.084
C-reactive protein, mg/dL	0.24 (0.08, 0.74)	0.31 (0.09, 1.28)	0.19 (0.06, 0.68)	0.143
<b>Level of consciousness</b>				
GCS score	9 (5, 12)	10 (8, 12)	9 (3, 12)	0.061
<b>Severity of general condition</b>				
SOFA score	5 (3, 7)	3 (2, 6)	5 (3, 7)	0.139

Data are expressed as medians (25<sup>th</sup> percentile, 75<sup>th</sup> percentile).

GCS: Glasgow Coma Scale; SOFA: Sequential Organ Failure Assessment

$^\dagger$ cerebral infarction vs. cerebral hemorrhage: Mann-Whitney's  $U$  test

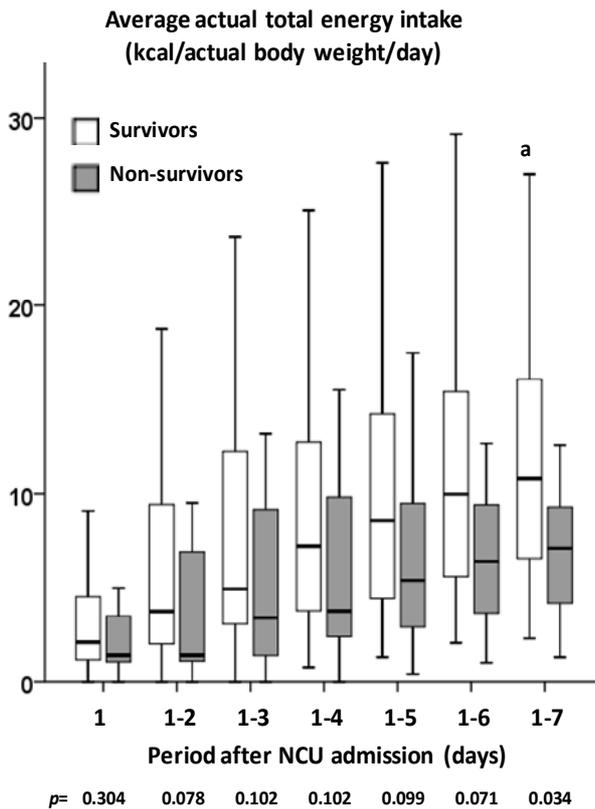
**Table 2.** Comparison of background characteristics between survivors and non-survivors

	Living status at 90 days after NCU admission		$p^\dagger$
	Survivor n = 75	Non-survivor n = 11	
<b>Demographics</b>			
Age, y	76.0 (62.0, 82.0)	81.0 (71.0, 90.0)	0.067
Gender			0.473
Men, % (n)	52.0 (39)	63.6 (7)	
<b>Cause of stroke</b>			
Cerebral infarction, % (n)	40.0 (30)	27.3 (3)	0.420
Cerebral hemorrhage, % (n)	60.0 (45)	72.7 (8)	
Body mass index, kg/m <sup>2</sup>	21.4 (19.9, 24.4)	22.2 (18.7, 24.5)	0.817
<b>Laboratory data</b>			
Hemoglobin, g/dL	13.1 (12.2, 14.4)	13.6 (12.5, 14.9)	0.660
Serum albumin, g/dL	4.0 (3.8, 4.3)	4.0 (3.8, 4.2)	0.881
<b>Level of consciousness</b>			
GCS score	9.0 (7.0, 12.0)	4.0 (3.0, 13.0)	0.105
<b>Severity of general condition</b>			
SOFA score	5.0 (3.0, 6.0)	8.0 (2.0, 9.0)	0.289
<b>Cumulative energy intake during first week in NCU</b>			
Total, kcal/kg/week	75.6 (45.5, 112.7)	49.7 (28.0, 77.0)	0.034
Enteral route, kcal/kg/week	53.9 (20.3, 84.0)	11.2 (0.0, 41.3)	0.008
Parenteral route, kcal/kg/week	17.5 (8.4, 36.4)	28.0 (9.1, 52.5)	0.569

Data are expressed as medians (25<sup>th</sup> percentile, 75<sup>th</sup> percentile).

GCS: Glasgow Coma Scale; NCU: Neurosurgical Care Unit; SOFA: Sequential Organ Failure Assessment

$^\dagger$ survivors vs. non-survivors: Mann-Whitney's  $U$  test



**Figure 1.** Comparison of average actual total energy intake between survivors and non-survivors. NCU: Neurosurgical Care Unit. a, Mann-Whitney's *U* test;  $p < 0.05$  (vs. non-survivors)

ure 3). This result suggests that energy intake administered through enteral route results in a difference in cumulative survival rate for 90 days after NCU admission in severely ill stroke patients.

## DISCUSSION

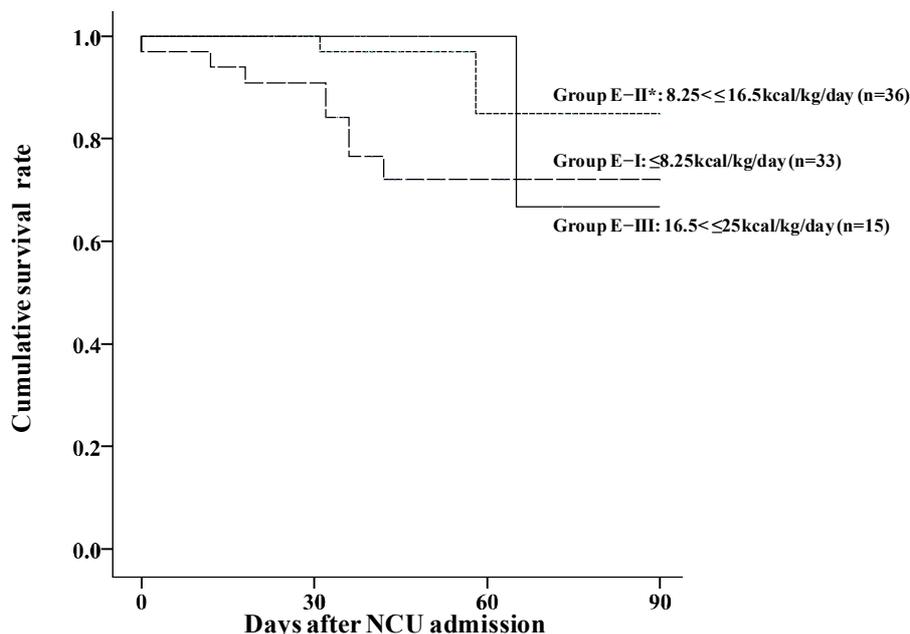
Stroke is one of main causes of death worldwide,<sup>1</sup> ranking as the third-leading cause of death in United States<sup>14</sup> and fourth-leading cause of death in Japan.<sup>2</sup> While opti-

mal nutritional support in intensive care unit (ICU) has been assessed with regard to intensive insulin therapy<sup>15</sup> and energy manipulations,<sup>13,16</sup> adequate nutritional support to improve clinical outcomes in stroke patients has not yet been clarified. Here, 86 consecutive stroke patients admitted to the NCU of a single neurological institute were analyzed to examine whether or not energy intake influences the survival rate 90 days after NCU admission.

As patients suffering less severe neurological injuries do not appear to require intensive nutritional support with long NCU stays until discharged, we limited our analysis to patients with severe neurological injury, defined by GCS scores lower than a cut-off point of 13.<sup>9</sup> In the present study, the GCS score did not differ between survivors and non-survivors (9.0 (7.0, 12.0) vs 4.0 (3.0, 13.0),  $p = 0.105$ , Table 2). This result suggests that mortality did not significantly differ among patients stratified by GCS score. In other words, when subjects were restricted only to those with severe neurological illness, the number of lower GCS score is not always associated with a higher mortality rate.

Given that our working hypothesis was that energy intake has an impact on the outcome of severely ill stroke patients, seven days might be necessary to observe a significant difference in average energy intake, as shown in Figure 1. This result might show that evaluation of the impact of energy intake on mortality requires at least the first seven days of assessment.

The question of which amount of energy intake most improves clinical outcomes of ICU patients remains controversial. Higher energy intake was reported to reduce mortality for 60 days and to increase the number of ventilator-free days,<sup>16</sup> while excessive energy intake is also reported to have adverse outcomes.<sup>13,17,18</sup> Energy intake of approximately 70% of target for first seven ICU days was shown to increase hospital mortality, mechanical ventilation duration and length of ICU and hospital stay.<sup>17</sup> Energy intake over 66% of the required value was also



**Figure 2.** Cumulative survival rate for 90 days after NCU admission. NCU: Neurosurgical Care Unit. \*Log rank test;  $p = 0.030$  (group E-II vs. group E-I).

**Table 3.** Hazard ratios of mortality for 90 days after NCU admission among groups categorized by average total energy intake for first seven NCU days

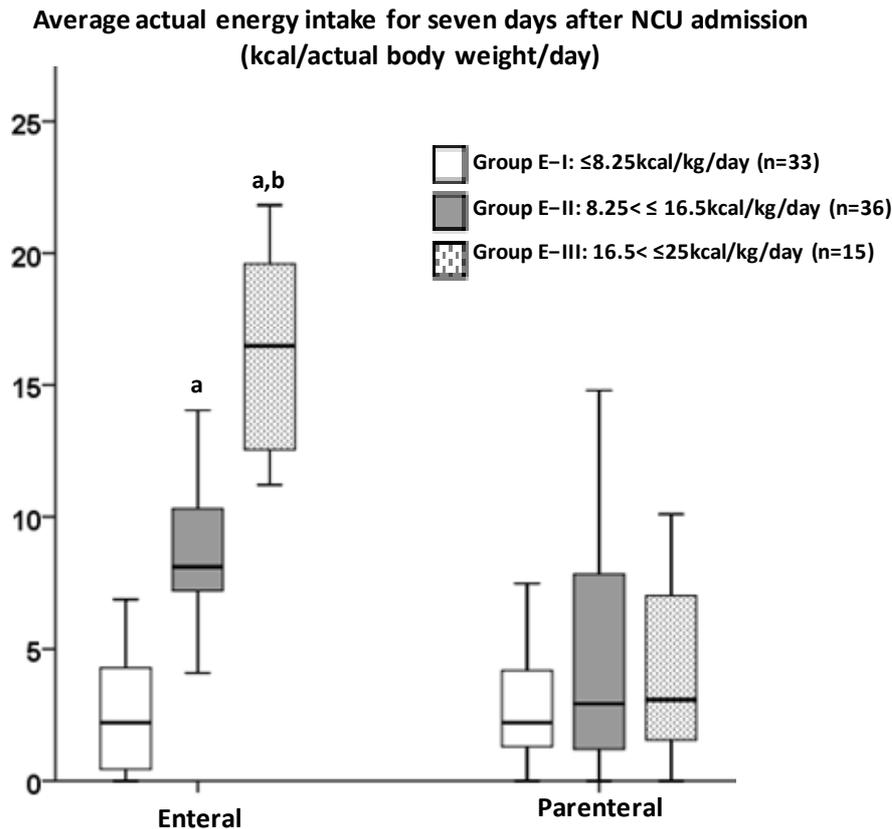
	Hazard ratio of mortality at 90 days			
	Crude	$p^{\ddagger}$	Adjusted <sup>†</sup>	$p^{\ddagger}$
Group E-I ( $\leq 8.25$ kcal/kg/day)	Ref		Ref	
Group E-II (8.25-16.5 kcal/kg/day)	0.21 (0.05, 1.00)	0.050	0.19 (0.04, 0.97)	0.047
Group E-III (16.5-25 kcal/kg/day)	0.55 (0.19, 1.55)	0.258	0.53 (0.17, 1.66)	0.279

Data are expressed as hazard ratios (95% confidence intervals).

NCU: Neurosurgical Care Unit

<sup>†</sup>Adjusted by age, C-reactive protein, and SOFA score.

<sup>‡</sup>Cox regression analysis.



**Figure 3.** Comparison of average actual energy intake by enteral and parenteral administration for the first seven NCU days among groups classified by average actual total energy intake for seven days after NCU admission. NCU: Neurosurgical Care Unit. a, Steel-Dwass test;  $p < 0.05$  (vs. group E-I). b, Steel-Dwass test;  $p < 0.05$  (vs. group E-II).

reported to be associated with higher mortality and longer ventilator management prior to ICU discharge.<sup>13</sup> In another report, hospital mortality was significantly lower with permissive underfeeding than with target feeding.<sup>18</sup>

On the other hand, it was reported that an energy deficit for seven days after ICU admission was strongly correlated with the length of mechanical ventilation, total number of complications, and length of ICU stay.<sup>19</sup> Other reports also show that low energy intake was significantly associated with an increased risk of bloodstream infections.<sup>20</sup> In our study, we observed that the cumulative survival rate for 90 days after NCU admission was significantly higher in group E-II (8.25-16.5 kcal/kg/day) than group E-I ( $\leq 8.25$  kcal/kg/day), which was set as the reference, although group E-III (16.5-25 kcal/kg/day) did not differ significantly (Figure 2). This result might suggest that the severely ill stroke patients in group E-III were overfed. However, confirmation of this possibility awaits further study in an increased number of patients.

With regard to providing an optimal amount of energy intake during the first seven days in severely ill stroke patients, we also analyzed the choice of nutritional routes. It has been reported that the enteral route reduces the mortality rate,<sup>21</sup> decreases the incidence of infections<sup>22</sup> and is the recommended route for nutritional support in critically ill patients treated in ICU.<sup>23,24</sup> In our study, only energy intake administered through the enteral route in group E-II significantly differed from those in groups E-I and E-III, although no difference was observed among the three groups with regard to parenterally administered energy intake. This result might be attributable to at least two possibilities: first, enterally administered energy might have provided a better survival rate for 90 days, as shown in Figure 2; and second, patients surviving in the NCU might have greater tolerance for enteral nutrition therapy than non-survivors owing to a hypoperfusion-associated decrease in gastrointestinal tolerance to enteral nutrition therapy. A definitive explanation awaits further large-scale prospective studies.

Several limitations of our present study warrant mention. First, the study was not conducted in a randomized fashion. Prospective studies with randomly allocated subjects are necessary to confirm optimal nutritional support for improving outcomes in patients with stroke as mentioned above. Second, the causes of stroke were limited to cerebral infarction and hemorrhage only, and subarachnoidal hemorrhage (SAH) was excluded because it has been reported to occur in younger populations. Additional analysis of patients with SAH might be undertaken to determine appropriate nutritional support for all causes of stroke. Third, the number of survivors and non-survivors was not well-balanced and patients' numbers in certain groups did not always allow for statistical significance. Although significant differences in energy intake during the first seven days of NCU admission between survivors and non-survivors were observed, these differences might have resulted from imbalances of patient numbers. Fourth, the GCS score cut-off of 13, which we applied for severely ill stroke patients, was obtained in a previous study in neurological trauma patients.<sup>9</sup> This cut-off value requires conclusive validation in patients with severe stroke. These limitations must be taken into account in any use of these findings to design optimal nutritional therapies for severely ill stroke patients.

In conclusion, our retrospective chart review suggests that the period of energy intake assessment required to determine the association of energy intake with stroke mortality is at least seven days. An average energy intake ranging between 8.25 and 16.5 kcal/kg/day for the first seven days after NCU admission and availability of administration via the enteral route appear to be associated with reduce mortality at 90 days in severely ill stroke patients.

#### AUTHOR DISCLOSURES

The authors report no conflicts of interest. Supported by grants from Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number 24700851).

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## Original Article

## Impact of energy intake on the survival rate of patients with severely ill stroke

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### 熱量攝取影響重症中風患者的存活率

前言：中風約佔全部死亡人數的 10%。本研究分析熱量攝取是否影響重症中風患者的存活率。方法：分析 86 位轉介的重症中風患者資料，比較存活者及非存活者的患者背景。收集進入神經外科加護病房(NCU)7 天內的熱量攝取，從第一天開始，每日累計，成 7 個時段，分別進行兩組比較，以找出哪個時段適合呈現熱量攝取差異。按照總熱量的攝取進行分層(層級別 E-I、E-II、E-III 及 E-IV，熱量分別為 $\leq 8.25$ 、8.25-16.5、16.5-25 及 $> 25$  大卡/公斤/天)，分析進入 NCU 90 天後之累積存活率。計算風險比(HR)和 95%信賴區間(CI)，以檢視干擾因子的影響。結果：在兩組之間，患者的背景沒有顯著差異；但非存活者在 NCU 的前 7 天，平均每日熱量攝取顯著低於存活者( $p=0.034$ )。E-II 層級的患者存活率顯著高於 E-I (參考組) ( $p=0.030$ )。在校正後，E-II 的風險比仍然顯著低於 E-I (HR=0.19,  $p=0.047$ )，在 E-III 則沒有顯著差異(HR=0.52,  $p=0.279$ )。結論：進入神經外科加護病房之後，應對患者進行至少 7 天的熱量攝取評估；重症的中風患者平均每日總熱量攝取 8.25-16.5 大卡/公斤以及腸道餵食，可能增加存活率。

關鍵字：中風、預後、熱量攝取、格拉斯哥昏迷量表、神經外科加護病房