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Research Article

Effect of Parenteral Energy or Amino Acid Doses on In-Hospital Mortality Among Patients With Aspiration Pneumonia: A Cohort Medical Claims Database Study

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Abstract

Background: This study examined the association between parenteral energy/amino acid doses and in-hospital mortality among inpatients on long-term nil per os (NPO) status, using a medical claims database in Japan.

Methods: Hospitalized patients with aspiration pneumonia, aged 65 and older, and on more than 7-day NPO status were identified in a medical claims database between January 2013 and December 2018. Using multivariate logistic regression and regression analyses, we examined the association between mean parenteral energy/amino acid doses and in-hospital mortality, and secondarily, the association between prognosis (in-hospital mortality, inability to receive full oral intake, readmission, and hospital stay length) and 4 groups of mean amino acid doses (no dose: 0 g/kg/day; very low dose: >0, ≤0.3 g/kg/day; low dose: >0.3, ≤0.6 g/kg/day; moderate dose: >0.6 g/kg/day).

Results: The analysis population included 20 457 inpatients (≥80 years: 78.3%). In total, 5 920 mortalities were recorded. Increased amino acid doses were significantly associated with reduced in-hospital mortality ($p < .001$). With a no dose reference level, the odds ratios (95% confidence interval) of in-hospital mortality adjusted for potential confounders were 0.78 (0.72–0.85), 0.74 (0.67–0.82), and 0.69 (0.59–0.81) for very low, low, and moderate amino acid doses, respectively. Additionally, patients prescribed amino acid dose levels more than 0.6 g/kg/day had shorter hospitalization periods than those prescribed none.

Conclusions: Increased amino acid doses were associated with reduced in-hospital mortality. Sufficient amino acid administration is recommended for patients with aspiration pneumonia requiring NPO status.

Keywords: Japan, Nil per os, Nutrition management, Real-world data

Aspiration pneumonia is a pulmonary system infection associated with dysphagia (1) and is strongly suspected to result from the inhalation of oropharyngeal or gastric contents into the respiratory organs causing pneumonia. It occurs more frequently in older adults and the frequency increases with age (2). Thus, in Japan, where the proportion of older adults (≥65 years) in the population is increasing, the incidence of aspiration pneumonia is expected to increase. The mortality rate associated with aspiration pneumonia is high. According to statistics published by the Ministry of Health, Labour and Welfare (2019), aspiration pneumonia is the sixth leading cause of death in Japan, causing mortality in 40 000 people annually (3). In a study of 66 000 patients hospitalized for the treatment of aspiration pneumonia at acute care hospitals in Japan, mortality at 30 days after hospitalization was 11.3% (4). Therefore, in aging populations such as those in Japan, identifying appropriate treatments and prevention measures is urgently needed. In addition to the conventional administration of antibiotics (5–7), diversified approaches to treat aspiration pneumonia have gained attention in recent decades (eg,

oral care, dysphagia rehabilitation, physical therapy, and nutritional management aimed at promoting recovery and preventing recurrence).

Nutrition management plays an important role in the treatment of aspiration pneumonia. This is because patients with aspiration pneumonia are generally older adults and at risk of malnutrition, dysphagia, and anorexia. Decreased skeletal muscle mass associated with malnutrition is also a risk factor for mortality among patients with aspiration pneumonia (8). An observational study of patients with aspiration pneumonia reported that early oral intake is associated with increased nutrient intake, improvement of swallowing function, and early recovery (9). Patients with aspiration pneumonia may, however, develop severe dysphagia and disturbed consciousness and, eventually, be placed on *nil per os* (NPO) status, for various time periods due to an inability to receive oral intake (10). In our previous study, 35% of 72 000 patients admitted to acute care hospitals for the treatment of aspiration pneumonia were placed on NPO status for longer than 7 days after admission (11). Although parenteral nutrition is commonly used for nutrition management of patients during NPO status, the median doses of parenteral energy and amino acid 7 days after hospitalization were very low and were 7.7 kcal/kg and 0.32 g/kg, respectively, possibly leading to poor prognosis due to malnutrition (11). To the best of our knowledge, however, there are no reports regarding the effect of prescribed nutrition doses on prognosis in patients with aspiration pneumonia placed on NPO status.

It is known that insufficient nutritional intake for inpatients at risk of malnutrition causes complications and mortality (12,13). In particular, patients with aspiration pneumonia who are placed on long-term NPO status are at a higher risk of malnutrition and have a worse prognosis than patients who achieve early oral intake (4,9). Therefore, increased nutritional prescription may contribute to improved prognosis. The study objective was to examine the association between parenteral energy/amino acid doses and in-hospital mortality among inpatients with aspiration pneumonia who have more than 7-day NPO status, using a medical claims database in Japan.

Method

Study Design and Data Source

The data for this retrospective cohort study were extracted from a medical claims database managed by Medical Data Vision Co., Ltd (MDV, Tokyo, Japan). The database covers approximately 22% of acute care hospitals in Japan and included information on approximately 26 million patients at 376 sites, as of December 2018. The MDV database includes information such as the date of hospitalization and discharge, age at the time of hospitalization, sex, height, body weight, diseases that led to hospitalization, comorbidities, activities of daily living, levels of consciousness, procedures during hospitalization, prescribed drugs (including various parenteral nutrition solutions and prescribed doses), and discharge status. Disease names were coded according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10 codes). Medical procedures were coded using Japan-specific medical claims codes.

Ethical Statements

Ethical approval was obtained from the Ethics and Conflict of Interest Committee of the National Center for Geriatrics and Gerontology (No. 1409). This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000041222). Individual patient informed consent was not obtained because all individuals' personal and site information used in this study were anonymized and classified as anonymously processed information under the Act on the Protection of Personal Information of 2003 as amended in 2020. Informed consent was not, therefore, required.

Patient Population

This study included patients aged 65 and older who were hospitalized for the treatment of aspiration pneumonia (ICD-10, J69) between January 2013 and December 2018 and who were placed on NPO status for more than 7 days. The following patients were excluded from the study: patients with suspected data entry errors for height or body weight values (height <100 cm, ≥200 cm, body weight <10 kg, ≥200 kg), patients with missing values for height or body weight, and patients with suspected data entry errors for prescribed parenteral nutrition solution doses or suspected to be in the terminal disease phase (no energy solutions were prescribed up to Day 7).

Endpoints

The primary endpoint was in-hospital mortality, and the secondary endpoints were prognosis (inability to receive full oral intake, readmission, and the length of hospital stay for discharged patients). Full oral intake was defined as 3 meals without enteral feeding or parenteral nutrition, and the proportion of patients who were unable to achieve full oral intake during hospitalization was calculated. Regarding readmission, the proportion of patients hospitalized within 30 days of discharge was calculated. The primary endpoint was examined among all patients and in 4 groups, as described below, and the secondary endpoints were examined in these 4 groups only.

Association Between Energy or Amino Acid Doses and In-Hospital Mortality

We examined the association between the mean doses of parenteral energy or amino acid and the frequency of in-hospital mortality. The daily doses of parenteral energy or amino acid per kilogram of body weight were calculated based on the ideal body weight for each day from Days 1 to 7. The daily dose was calculated from all prescribed energy and amino acid doses. Energy was calculated based not only on nutrition solution administration, but also on the general anesthetic/sedative propofol, which is dissolved in a lipid emulsion, glucose solutions used for the preparation of drugs, maintenance solutions, and extracellular fluids with added carbohydrates.

Association Between Amino Acid Doses and Prognosis

We also examined the association between prognosis and the administered parenteral amino acid doses on Days 1–7 among 4 groups. Patients were divided into 4 groups according to the mean amino acid dose on Days 1–7: no dose (0 g/kg/day), very low dose (>0, ≤0.3 g/kg/day), low dose (>0.3, ≤0.6 g/kg/day), and moderate dose (>0.6 g/kg/day). Parenteral amino acid doses were analyzed in these groups because this parameter was found to be associated with in-hospital mortality in the overall analysis described above. For each group, the patient characteristics described below were extracted, and changes in the parenteral energy and amino acid doses during NPO status were calculated based on the ideal body weight for each day from Days 1 to 30 during the hospitalization stay.

Baseline Characteristics

The following patient characteristics were extracted from the MDV database: age on Day 1, sex, height, body weight, number of hospital beds, treatment year, comorbidities, dementia, Parkinson's disease, cancer, Barthel Index (14), Japan Coma Scale (15), intensive care unit admission, and oxygen inhalation on Day 1. In addition, the following characteristics were extracted from Days 1 to 7: nutrition support team intervention, dysphagia rehabilitation, other types of rehabilitation (for cardiovascular diseases, cerebrovascular diseases, disuse syndrome, motor disease, and respiratory disease), and mean parenteral energy and amino acid administration.

Patients were divided into age groups of 65–69 years, 70–79 years, 80–89 years, and 90 years or older. Body mass index (BMI) was calculated based on height and body weight and classified into the following groups: <16, 16 to <18.5, 18.5 to <22.5, 22.5 to <25, and ≥25, according to the World Health Organization classification. The study sites were divided by the number of hospital beds into groups of <200, 200 to <500, and ≥500 beds. The Charlson Comorbidity Index was calculated for comorbidities using the algorithm developed by Quan et al. (16) and divided into 0, 1–2, and ≥3. Activities of daily living were represented by Barthel Index values ranging from 0 (full assistance) to 100 (full independence) (14) and divided into 0, 5–20, 25–40, 45–60, 65–95, and 100. The level of consciousness was represented by the Japan Coma Scale with 0 (alert), 1-digit number (not fully alert but awake without any stimuli), 2-digit number (arousable with stimulation), and 3-digit number (unarousable) (15). Missing values in the Barthel Index and the Japan Coma Scale were handled as missing.

Statistical Analysis

Frequencies and percentages were summarized for categorical variables, and continuous variables were summarized by median and interquartile ranges (first quartile [Q1], third quartile [Q3]).

To examine the association between energy or amino acid doses and in-hospital mortality, a multivariate logistic model was used with in-hospital mortality as the response variable, and mean parenteral energy or amino acid doses on Days 1–7 as the explanatory variable adjusted for the baseline patient characteristics (age, sex, BMI, number of hospital beds, treatment year, Charlson Comorbidity Index, dementia, Parkinson's disease, cancer, Barthel Index, Japan Coma Scale, intensive care unit admission status [Day 1], oxygen inhalation [Day 1], nutrition support team intervention [Days 1–7], dysphagia rehabilitation [Days 1–7], other types of rehabilitation [Days 1–7], mean dose of amino acid or mean dose of energy [Days 1–7]). Modeling for multivariate logistic regression analyses was conducted after confirming the variance inflation factor (Supplementary Table 1). The odds ratios of all variables are also presented (Supplementary Table 2). A theoretical curve was plotted for adjusted odds ratios with 95% lower or upper control limits where the energy doses were shown in 1 kcal/kg/day increments up to 0–20 kcal/kg/day. Similarly, a theoretical curve was shown in 0.1 g/kg/day increments up to 0–1.2 g/kg/day.

Regarding the statistical testing for baseline characteristics and each of 4 endpoints among groups classified by amino acid doses, the Chi-square test or Kruskal–Wallis test was used. To examine the association between amino acid doses and in-hospital mortality, inability to receive full oral intake, or readmission, multivariate logistic regression analysis was performed. For evaluation of the length of hospital stay among amino acid doses group, a multivariate regression analysis was performed. Multivariate logistic regression analyses and regression analyses were adjusted for the same patient baseline characteristics described above, and unadjusted and adjusted results were presented (Supplementary Table 3). Based on the number of days from Day 1 to the day of in-hospital mortality, the hazard ratios were calculated using the Cox proportional hazard model. All analyses were adjusted for the same patient baseline characteristics described above. Discharged patients and patients hospitalized for at least 90 days were censored. The adjusted odds ratios, estimates, hazard ratios, and 95% confidence intervals (CIs) for each group were calculated using the no-dose as the reference level.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) at a 2-sided significance level of 5%.

Results

Baseline Patient Characteristics

Among all patients included in this study, 20 457 did not meet any exclusion criteria (Figure 1). Patient characteristics are given in Table 1. Among the 20 457 patients included, 78.3% were 80 years or older, 55.0% were men, and 52.7% had a BMI of less than 18.5. Among these patients, 69.8% required full assistance (Barthel Index = 0), 62.0% had disturbed consciousness (Japan Coma Scale ≥1), and 69.1% were on oxygen inhalation. The median (first quartile [Q1], third quartile [Q3]) of the mean parenteral energy dose was 5.9 (3.7–8.3) kcal/kg/day on Days 1–7, and the amino acid dose was 0.20 (0.00–0.45) g/kg/day. The overall number of mortalities was 5 920 (28.9%).

Association Between Energy and Amino Acid Doses and In-Hospital Mortality

Figure 2 shows the relationship between and adjusted odds ratios (95% CI) for in-hospital mortality and mean energy/amino acid doses on Days 1–7. There was a significant association between increased amino acid dose and reduced in-hospital mortality (Wald test, $p < .001$), but no association was noted between increased energy doses and in-hospital mortality (Wald test, $p = .19$).

Patient Characteristics and Changes in Prescribed Nutrition Doses According to Amino Acid Dose

The patient characteristics of each amino acid group are given in Table 1. The median of the mean amino acid dose from Days 1 to 7 was 0.22 (0.14–0.26) g/kg/day for the very low dose, 0.46 (0.37–0.52) g/kg/day for the low dose, and 0.69 (0.64–0.77) g/kg/day for the moderate dose. Figure 3 shows the changes in parenteral energy and amino acid doses during NPO status in each group.

Prognosis According to Amino Acid Doses

The distribution of each endpoint is given in Table 2 (A). The percentage of in-hospital mortality was 32.8% for no dose, 28.1% for very low dose, 26.3% for low dose, and 24.0% for moderate dose (Chi-square test, $p < .001$).

The results of multivariate logistic regression and regression analyses in which each endpoint was adjusted for background patient characteristics are given in Table 2 (B). The odds ratios (95% CI) of in-hospital mortality with a reference of no dose were 0.78 (0.72–0.85) for very low dose, 0.74 (0.67–0.82) for low dose, and 0.69 (0.59–0.81) for moderate dose. There was no statistically significant difference in the risks of inability to receive oral intake or readmission in each group. The estimates (95% CI) of the length of

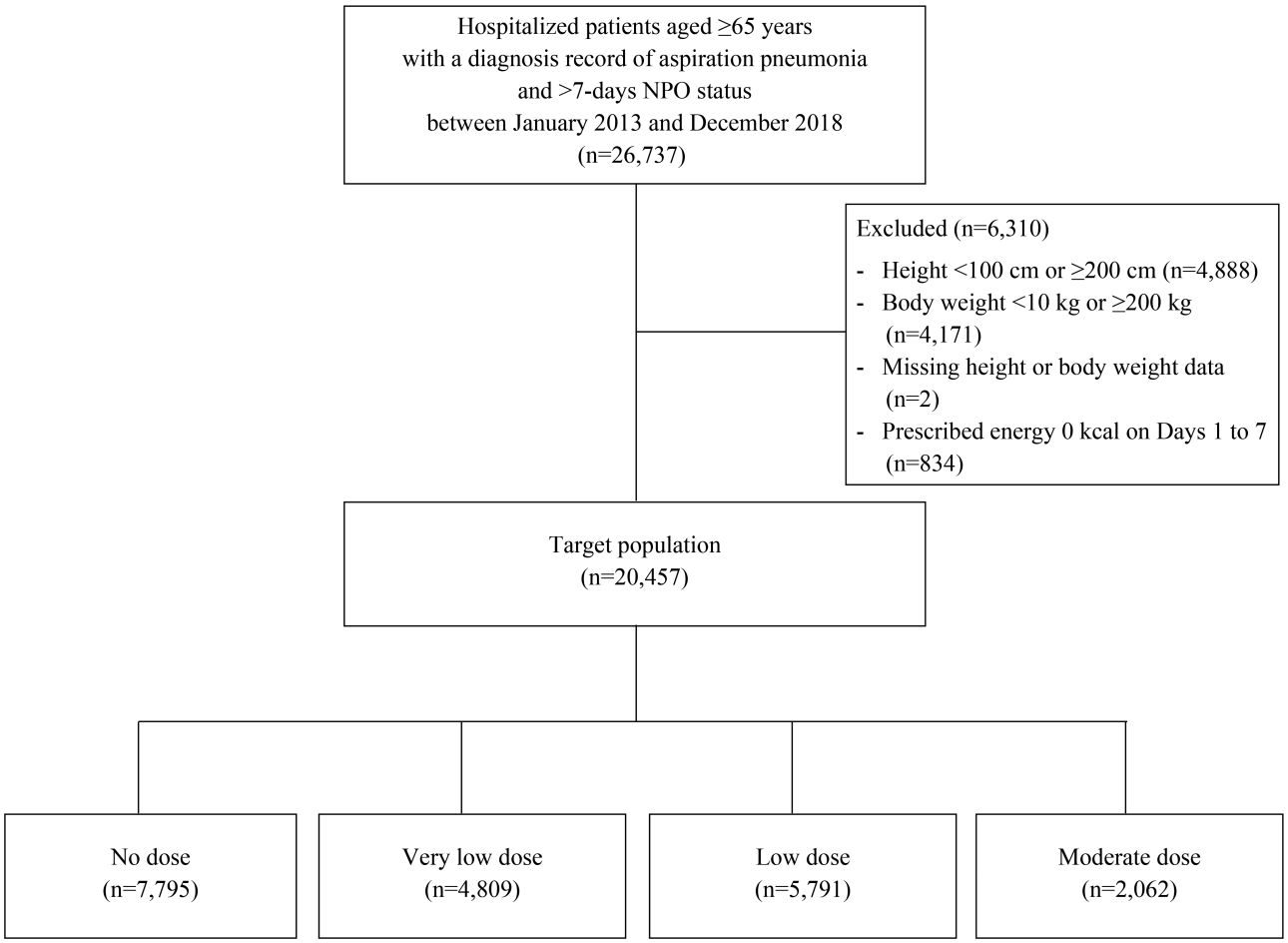


Figure 1. Patient flow. NPO = nil per os.

hospital stay, adjusted for background patient characteristic with a reference of no dose, were as follows: very low dose, 1.31 (−0.25 to 2.87); low dose, −0.25 (−2.02 to 1.52); and moderate dose, −4.53 (−7.30 to −1.76). Cox proportional hazard analysis showed that the hazard ratios (95% CI) adjusted for no dose were 0.80 (0.74–0.86), 0.81(0.75–0.89), and 0.88 (0.76–1.01) for very low, low, and moderate doses, respectively.

Discussion

This is the first large-scale study to examine the hypothesis that an increased amount of prescribed parenteral energy or amino acid reduces the risk of in-hospital mortality in patients with aspiration pneumonia who have a greater than 7-day NPO status. An association was found between increased amino acid doses and reduced in-hospital mortality, but no association was found between increased energy doses and in-hospital mortality. Among 4 groups of patients administered various amino acid doses, the odds of in-hospital mortality in the very low dose (>0, ≤0.3 g/kg/day), low dose (> 0.3, ≤0.6 g/kg/day), and moderate dose (>0.6 g/kg/day) groups were significantly lower than that in the no-dose group. The length of hospital stay was significantly shorter in the moderate-dose group than in the no-dose group.

The results of this study showed that the prescribed energy doses were markedly low from Days 1 to 7 (median energy dose of 5.9 kcal/kg/day), which is lower than the recommended dose of ≥20 kcal/kg/day (17). Furthermore, an increase in the energy dose did not contribute to decreased in-hospital mortality among this study population. A previous observational study of patients with pneumonia, however, reported that increased intake of energy until Day 7 was associated with reduced mortality (18). Our results may have differed from those from this study due to differences in patient characteristics; patients included in our study had been placed on long-term NPO status without oral intake, whereas patients in the previous study were predominantly able to orally ingest food. Severe pneumonia, low daily living activities, low levels of consciousness, and low BMI have been reported as risk factors for long-term NPO status in patients with aspiration pneumonia (4,11). As our target study population included patients with long-term NPO status, the mortality rate was higher compared to the aforementioned study, because a greater proportion of patients with high disease severity was included in the current study.

The results of multicenter, randomized, clinical trials investigating the effects of different calorie intakes on prognosis in critically ill patients have reported that low calorie intakes do not affect mortality (19,20). It has, however, been reported that infectious complications increase when the energy dose is insufficient for a long time period and the deficit exceeds 10 000 kcal (21). Our study did not investigate mortality outside of hospitals and associations with long-term insufficient energy doses. Additionally, as we used real-world data

Table 1. Patient Characteristics

			Amino Acid				
		Total	No Dose*	Very Low Dose*	Low Dose*	Moderate Dose*	
		n = 20 457	*n* = 7 795	*n* = 4 809	*n* = 5 791	*n* = 2 062	*p*†
Age, years	65–69	697 (3.4)	225 (2.9)	177 (3.7)	205 (3.5)	90 (4.4)	<.001
	70–79	3 752 (18.3)	1 263 (16.2)	925 (19.2)	1 179 (20.4)	385 (18.7)	
	80–89	9 855 (48.2)	3 735 (47.9)	2 338 (48.6)	2 844 (49.1)	938 (45.5)	
	≥90	6 153 (30.1)	2 572 (33.0)	1 369 (28.5)	1 563 (27.0)	649 (31.5)	
Sex	Male	11 247 (55.0)	4 107 (52.7)	2 952 (61.4)	3 337 (57.6)	851 (41.3)	<.001
	Female	9 210 (45.0)	3 688 (47.3)	1 857 (38.6)	2 454 (42.4)	1 211 (58.7)	
Body mass index, kg/m²	<16	5 067 (24.8)	1 779 (22.8)	1 230 (25.6)	1 538 (26.6)	520 (25.2)	<.001
	16–18.5	5 714 (27.9)	2 173 (27.9)	1 326 (27.6)	1 628 (28.1)	587 (28.5)	
	18.5–22.5	6 925 (33.9)	2 727 (35.0)	1 636 (34.0)	1 880 (32.5)	682 (33.1)	
	22.5–25	1 829 (8.9)	714 (9.2)	422 (8.8)	511 (8.8)	182 (8.8)	
	≥25	922 (4.5)	402 (5.2)	195 (4.1)	234 (4.0)	91 (4.4)	
Number of hospital beds	<200	2 862 (14.0)	1 187 (15.2)	679 (14.1)	751 (13.0)	245 (11.9)	<.001
	≥200, <500	13 191 (64.5)	4 958 (63.6)	3 174 (66.0)	3 736 (64.5)	1 323 (64.2)	
	≥500	4 404 (21.5)	1 650 (21.2)	956 (19.9)	1 304 (22.5)	494 (24.0)	
Treatment year	2013	2 170 (10.6)	701 (9.0)	515 (10.7)	675 (11.7)	279 (13.5)	<.001
	2014	2 883 (14.1)	1 076 (13.8)	703 (14.6)	792 (13.7)	312 (15.1)	
	2015	3 379 (16.5)	1 281 (16.4)	756 (15.7)	954 (16.5)	388 (18.8)	
	2016	3 841 (18.8)	1 532 (19.7)	896 (18.6)	1 047 (18.1)	366 (17.7)	
	2017	4 097 (20.0)	1 575 (20.2)	970 (20.2)	1 189 (20.5)	363 (17.6)	
	2018	4 087 (20.0)	1 630 (20.9)	969 (20.1)	1 134 (19.6)	354 (17.2)	
Charlson Comorbidity Index	0	10 008 (48.9)	3 732 (47.9)	2 362 (49.1)	2 912 (50.3)	1 002 (48.6)	<.001
	1–2	7 959 (38.9)	3 043 (39.0)	1 851 (38.5)	2 233 (38.6)	832 (40.3)	
	≥3	2 490 (12.2)	1 020 (13.1)	596 (12.4)	646 (11.2)	228 (11.1)	
Dementia		5 153 (25.2)	2 000 (25.7)	1 181 (24.6)	1 436 (24.8)	536 (26.0)	.376
Parkinson's disease		1 347 (6.6)	505 (6.5)	314 (6.5)	400 (6.9)	128 (6.2)	.654
Cancer		2 049 (10.0)	742 (9.5)	492 (10.2)	583 (10.1)	232 (11.3)	.117
Barthel Index	100	483 (2.4)	176 (2.3)	112 (2.3)	143 (2.5)	52 (2.5)	<.001
	65–95	270 (1.3)	76 (1.0)	70 (1.5)	92 (1.6)	32 (1.6)	
	45–60	561 (2.7)	194 (2.5)	133 (2.8)	177 (3.1)	57 (2.8)	
	25–40	469 (2.3)	180 (2.3)	116 (2.4)	130 (2.2)	43 (2.1)	
	5–20	1 915 (9.4)	737 (9.5)	482 (10.0)	521 (9.0)	175 (8.5)	
	0	14 283 (69.8)	5 558 (71.3)	3 329 (69.2)	3 997 (69.0)	1 399 (67.8)	
	NA	2 476 (12.1)	874 (11.2)	567 (11.8)	731 (12.6)	304 (14.7)	
Japan Coma Scale	0	7 765 (38.0)	2 912 (37.4)	1 788 (37.2)	2 249 (38.8)	816 (39.6)	<.001
	1–3	7 108 (34.7)	2 603 (33.4)	1 719 (35.7)	2 073 (35.8)	713 (34.6)	
	10–30	3 913 (19.1)	1 539 (19.7)	911 (18.9)	1 079 (18.6)	384 (18.6)	
	100–300	1 670 (8.2)	740 (9.5)	391 (8.1)	390 (6.7)	149 (7.2)	
	NA	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Intensive care unit admission‡	Yes	1 627 (8.0)	661 (8.5)	400 (8.3)	441 (7.6)	125 (6.1)	<.01
Oxygen inhalation‡	Yes	14 133 (69.1)	5 553 (71.2)	3 318 (69.0)	3 923 (67.7)	1 339 (64.9)	<.001
Nutrition support team intervention§	Yes	702 (3.4)	209 (2.7)	168 (3.5)	223 (3.9)	102 (4.9)	<.001
Dysphagia rehabilitation§	Yes	3 551 (17.4)	1 274 (16.3)	938 (19.5)	1 020 (17.6)	319 (15.5)	<.001
Other types of rehabilitation§,‖	Yes	8 723 (42.6)	3 195 (41.0)	2 131 (44.3)	2 516 (43.4)	881 (42.7)	<.01
Energy, kcal/kg/day¶, median (Q1–Q3)		5.9 (3.7–8.3)	3.5 (2.6–4.6)	5.5 (4.4–6.8)	7.9 (6.8–9.4)	10.8 (9.5–13.1)	<.001
Amino acid, g/kg/day¶, median (Q1–Q3)		0.20 (0.00–0.45)	—	0.22 (0.14–0.26)	0.46 (0.37–0.52)	0.69 (0.64–0.77)	<.001

Notes: Q1 = first quartile; Q3 = third quartile. All numbers are expressed with number (%) unless otherwise stated.

*Classification according to the mean dose of parenteral amino acid on Days 1–7: no dose (0 g/kg/day), very low dose (>0, ≤0.3 g/kg/day), low dose (>0.3, ≤0.6 g/kg/day), and moderate dose (>0.6 g/kg/day).

†Chi-square tests for all analyses except for energy and amino acids whose tests were Kruskal–Wallis tests.

‡On Day 1.

§On Days 1–7.

‖This rehabilitation is for cardiovascular disease, cerebrovascular disease, disuse syndrome, motor disease, or respiratory disease.

¶Mean from Days 1 to 7.

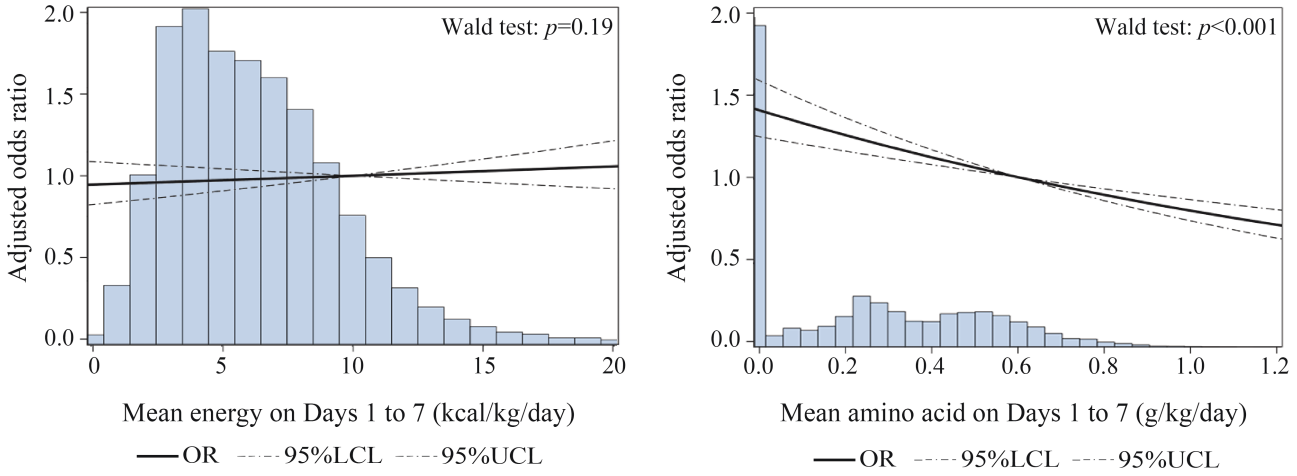
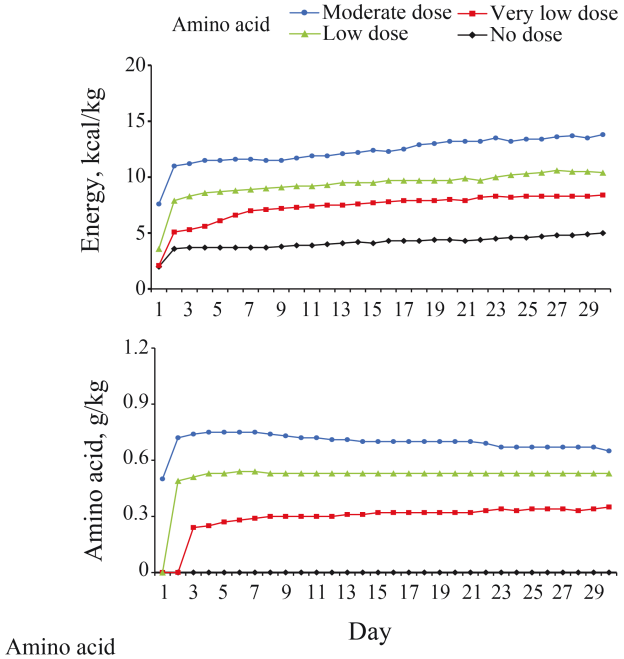


Figure 2. Theoretical curves of adjusted odds ratio for in-hospital mortality based on multivariate logistic regression analysis with respect to mean parenteral energy and amino acid doses on Days 1–7.



Amino acid					
Moderate dose	2,062	2,062	987	705	534
Low dose	5,791	5,791	2,795	1,988	1,520
Very low dose	4,809	4,809	2,215	1,550	1,211
No dose	7,795	7,795	3,446	2,400	1,788

Figure 3. Changes in parenteral energy and amino acid doses (median) during nil per os status.

and administration of energy doses were generally insufficient in our study, we could not fully examine the effects of sufficient energy doses on prognosis. In the future, it may be necessary to examine the effect of energy dose administration on prognoses other than mortality and the effect of long-term insufficient and sufficient energy dose administration on prognosis.

Our study also confirmed that increases in parenteral amino acid doses were associated with decreased in-hospital mortality. Parenteral nutrition guidelines for older adults (age >65 years) state that the majority of this population with diseases require at least 1.0–1.2 g/kg/day of amino acid doses (17). It has also been suggested that higher amino acid doses (1.2–2.0 g/kg/day) are required in malnourished older adults to improve the nitrogen balance and restore lean body mass (22,23). In our study, 78.3% of patients investigated were on NPO status for more than 7 days and aged 80 and older, 52.7% had a BMI less than 18.5, and 69.8% had a Barthel Index score = 0 (full assistance). These results indicate that our study included a greater proportion of malnourished patients or patients at a high risk of malnutrition. With aspiration pneumonia, acute inflammation causes muscular atrophy of the respiratory, skeletal, and swallowing systems (24). Disuse muscle atrophy associated with bed rest can also develop in patients with reduced daily living activities, which may lead to reduced skeletal muscle mass and progression of sarcopenia (25). Decreased skeletal muscle mass due to malnutrition is a risk factor for mortality in patients with aspiration pneumonia (8), and patients with aspiration pneumonia who are on long-term NPO status may, therefore, require higher amino acid doses than recommended in the parenteral nutrition guidelines for older adults (1.0–1.2 g/kg/day). In this study, however, only 2 062 of 20 457 patients (~10%) were prescribed amino acid more than 0.6 g/kg/day, and it was not possible to conduct a detailed evaluation of patients prescribed amino acid at higher dose levels (eg, up to ~2.0 g/kg/day). In the future, it would be informative to investigate the optimal amino acid dose in terms of efficacy and safety in a prospective study.

Limitations of the Study

This study has several limitations. First, using a medical claims database in this study may have led to data entry errors, missing values, and accuracy problems, which were not possible to control. The disease differentiation accuracy in our study was inferior to that of prospective studies. Several published studies in which aspiration pneumonia was identified using the ICD-10 code (J 69) (4,26,27) and other disease codes for scoring the Charlson Comorbidity Index (28) have already been conducted, and these disease codes have been previously validated. Second, the pneumonia severity classification (A-DROP) (29), an index for predicting prognosis, could not be used in this study because some information was unavailable in the database. However, of the 5 items used in the A-DROP classification (age, dehydration, respiratory failure, disturbed consciousness [orientation], hypotension [pressure]), we obtained information on 3 of these items: age, disturbed consciousness (Japan Coma Scale), and respiratory failure (oxygen inhalation). We used these items as

Table 2. (A) Distribution of Endpoints and (B) Results of Multivariate Logistic Regression and Regression Analyses Adjusted for Baseline Characteristics

	Amino acid				
(A)	No Dose*	Very Low Dose*	Low Dose*	Moderate Dose*	
Prognosis	*n* = 7 795	*n* = 4 809	*n* = 5 791	*n* = 2 062	*p*
In-hospital mortality, *n* (%)	2 554 (32.8)	1 350 (28.1)	1 521 (26.3)	495 (24.0)	<.001†
Inability to receive full oral intake, *n* (%)‡,§	2 028 (38.7)	1 178 (34.1)	1 373 (32.2)	473 (30.2)	<.001†
Readmission, *n* (%)§	310 (5.9)	242 (7.0)	222 (5.2)	71 (4.5)	<.001†
Length of hospital stay, median (Q1–Q3)§	33 (22–50)	35 (24–55)	35 (24–54)	32 (22–50)	<.001‖
(B)					
Prognosis	**Odds Ratio or Estimates (95% CI), Adjusted¶**				
In-hospital mortality	Reference	0.78 (0.72 to 0.85)	0.74 (0.67 to 0.82)	0.69 (0.59 to 0.81)	—
Inability to receive full oral intake‡,§	Reference	0.94 (0.85 to 1.04)	0.94 (0.84 to 1.05)	0.88 (0.74 to 1.05)	—
Readmission§	Reference	1.19 (0.99 to 1.44)	0.89 (0.71 to 1.11)	0.84 (0.58 to 1.22)	—
Length of hospital stay§	Reference	1.31 (−0.25 to 2.87)	−0.25 (−2.02 to 1.52)	−4.53 (−7.30 to −1.76)	—

Notes: Q1 = first quartile; Q3 = third quartile; CI = confidence interval.

*Classification according to the mean dose of parenteral amino acid on Days 1–7: no dose (0 g/kg/day), very low dose (>0, ≤0.3 g/kg/day), low dose (>0.3, ≤0.6 g/kg/day), and moderate dose (>0.6 g/kg/day).

†Chi-square tests.

‡Oral intake of 3 meals without enteral feeding or parenteral nutrition.

§Of those patients discharged alive (no dose: *n* = 5 241; very low dose: *n* = 3 459; low dose: *n* = 4 270; moderate dose: *n* = 1 567).

‖Kruskal–Wallis test.

¶Adjusted variables were age, sex, BMI, number of hospital beds, treatment year, Charlson Comorbidity Index, dementia, Parkinson's disease, cancer, Barthel Index, Japan Coma Scale, intensive care unit admission status (Day 1), oxygen inhalation (Day 1), nutrition support team intervention (Days 1–7), dysphagia rehabilitation (Days 1–7), other types of rehabilitation (Days 1–7), and mean energy (Days 1–7).

adjustment variables along with other patient background factors that may affect patient prognosis. Third, there is no information on unused and wasted infusion solution doses and, therefore, the actual administered parenteral nutrition doses may have been lower than the prescribed doses calculated in this study. Fourth, the study included patients admitted to institutions participating in diagnosis procedure combination/per-diem payment system (mostly acute care hospitals); our results may not be generalizable to patients admitted to long-term care hospitals in Japan. Finally, patients in this database included only those who received inpatient or ambulatory treatment at the institution where they were admitted for the treatment of aspiration pneumonia; thus, cases of readmission in other institutions may be underestimated. These limitations should be noted when interpreting the results of the present study.

Conclusions

This study examined the association between energy or amino acid doses up to 7 days after hospitalization and prognosis among patients with aspiration pneumonia who were placed on more than 7-day NPO status. An increased amino acid dose was associated with reduced in-hospital mortality. In addition, patients who were prescribed amino acid dose levels more than 0.6 g/kg/day had shorter hospitalization periods than those prescribed no amino acid. These results indicate that special attention should be given to the management of parenteral nutrition to avoid insufficient administration of amino acids. Further studies may clarify the optimal energy and amino acid doses to improve the prognosis of patients with aspiration pneumonia.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

The authors declare the following financial interests/personal relationships: K.M. has received a research fund and lecture fees from Otsuka Pharmaceutical Factory, Inc. S.K., Y.H., and A.K. are employees of Otsuka Pharmaceutical Factory, Inc. K.Mu. declares no conflict of interest.

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Author Contributions

All authors made substantial contributions to all of the following: (a) the conception and design of the study, acquisition of data, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be submitted and meeting the ICMJE authorship criteria.

References

1. Kohno S, Imamura Y, Shindo Y, et al. Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP) [complete translation]. *Respir Investig*. 2013;51(2):103–126. doi:10.1016/j.resinv.2012.11.001
2. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. *Respir Investig*. 2015;53(5):178–184. doi:10.1016/j.resinv.2015.01.003

3. Ministry of Health Law. 2019 Summary of vital statistics 2020 [in Japanese]. Accessed November 2020. https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai19/index.html
4. Momosaki R, Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Abo M. Predictive factors for oral intake after aspiration pneumonia in older adults. *Geriatr Gerontol Int*. 2016;16(5):556–560. doi:10.1111/ggi.12506
5. DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. *J Crit Care*. 2015;30(1):40–48. doi:10.1016/j.jcrc.2014.07.011
6. Momosaki R. Rehabilitative management for aspiration pneumonia in elderly patients. *J Gen Fam Med*. 2017;18(1):12–15. doi:10.1002/jgf2.25
7. Mandell LA, Niederman MS. Aspiration pneumonia. *N Engl J Med*. 2019;380(7):651–663. doi:10.1056/NEJMra1714562
8. Maeda K, Akagi J. Muscle mass loss is a potential predictor of 90-day mortality in older adults with aspiration pneumonia. *J Am Geriatr Soc*. 2017;65(1):e18–e22. doi:10.1111/jgs.14543
9. Maeda K, Koga T, Akagi J. Tentative nil per os leads to poor outcomes in older adults with aspiration pneumonia. *Clin Nutr*. 2016;35(5):1147–1152. doi:10.1016/j.clnu.2015.09.011
10. Kenzaka T, Kosami K, Matsuoka Y, Noda A, Kumabe A. The difference between ideal and actual fasting duration in the treatment of patients with aspiration pneumonia: a nationwide survey of clinicians in Japan. *Tohoku J Exp Med*. 2016;240(3):227–233. doi:10.1620/tjem.240.227
11. Maeda K, Murotani K, Kamoshita S, Horikoshi Y, Kuroda A. Nutritional management in inpatients with aspiration pneumonia: a cohort medical claims database study. *Arch Gerontol Geriatr*. 2021;95:104398. doi:10.1016/j.archger.2021.104398
12. Schuetz P, Fehr R, Baechli V, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet*. 2019;393(10188):2312–2321. doi:10.1016/S0140-6736(18)32776-4
13. Gomes F, Baumgartner A, Bounoure L, et al. Association of nutritional support with clinical outcomes among medical inpatients who are malnourished or at nutritional risk: an updated systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(11):e1915138. doi:10.1001/jamanetworkopen.2019.15138
14. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61–65.
15. Shigematsu K, Nakano H, Watanabe Y. The eye response test alone is sufficient to predict stroke outcome—reintroduction of Japan Coma Scale: a cohort study. *BMJ Open*. 2013;3(4):e002736. doi:10.1136/bmjopen-2013-002736
16. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682. doi:10.1093/aje/kwq433
17. Sobotka L, Schneider SM, Berner YN, et al.; ESPEN. ESPEN guidelines on parenteral nutrition: geriatrics. *Clin Nutr*. 2009;28(4):461–466. doi:10.1016/j.clnu.2009.04.004
18. Shirado K, Wakabayashi H, Maeda K, et al. Impact of energy intake at one week after hospitalization on prognosis for older adults with pneumonia. *J Nutr Health Aging*. 2020;24(1):119–124. doi:10.1007/s12603-019-1282-y
19. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795–803. doi:10.1001/jama.2012.137.
20. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med*. 2015;372(25):2398–2408. doi:10.1056/NEJMoa1502826
21. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr*. 2005;24(4):502–509. doi:10.1016/j.clnu.2005.03.006
22. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. *Clin Nutr*. 2008;27(5):675–684. doi:10.1016/j.clnu.2008.06.008
23. Baum JI, Kim IY, Wolfe RR. Protein consumption and the elderly: what is the optimal level of intake? *Nutrients*. 2016;8(6):359. doi:10.3390/nu8060359
24. Komatsu R, Okazaki T, Ebihara S, et al. Aspiration pneumonia induces muscle atrophy in the respiratory, skeletal, and swallowing systems. *J Cachexia Sarcopenia Muscle*. 2018;9(4):643–653. doi:10.1002/jcsm.12297
25. Fujishima I, Fujiu-Kurachi M, Arai H, et al. Sarcopenia and dysphagia: position paper by four professional organizations. *Geriatr Gerontol Int*. 2019;19(2):91–97. doi:10.1111/ggi.13591
26. Momosaki R, Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Abo M. Effect of early rehabilitation by physical therapists on in-hospital mortality after aspiration pneumonia in the elderly. *Arch Phys Med Rehabil*. 2015;96(2):205–209. doi:10.1016/j.apmr.2014.09.014
27. Chang CY, Cheng TJ, Lin CY, Chen JY, Lu TH, Kawachi I. Reporting of aspiration pneumonia or choking as a cause of death in patients who died with stroke. *Stroke*. 2013;44(4):1182–1185. doi:10.1161/STROKEAHA.111.000663
28. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol*. 2017;27(10):476–482. doi:10.1016/j.je.2016.09.009
29. Miyashita N, Matsushima T, Oka M; Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. *Intern Med*. 2006;45(7):419–428. doi:10.2169/internalmedicine.45.1691