

Predictors of Discontinuance of Oral Feeding in Patients With Advanced Alzheimer Dementia and Aspiration Pneumonia in Japan

A Single-center, Retrospective Observational Study

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Background: Difficulty with oral feeding, the most commonly observed complication of Alzheimer disease (AD) in its final stages, occurs in 86% of AD patients and may prevent achievement of oral feeding after aspiration pneumonia. However, no reliable indicators of discontinuance of oral feeding have yet been identified. We therefore aimed to identify predictors of discontinuance of oral feeding in postaspiration pneumonia patients with AD.

Materials and Methods: Relevant clinical and laboratory data of 60 patients with AD admitted to our hospital in Japan for aspiration pneumonia were retrospectively compared between oral feeding and discontinuance groups.

Results: The study groups differed in interval since diagnosis of AD, CURB-65 score, pneumonia severity index score, and proportion of patients who died (higher in the discontinuance group) and body mass index (BMI), Mini Mental State Examination (MMSE) score, and functional independence measure score (lower in the discontinuance group). According to multivariate logistic regression analysis of all identified independent variables, only CURB-65 and MMSE scores and BMI are significant predictors of discontinuance of oral feeding after aspiration pneumonia in patients with advanced AD.

Conclusions: In patients with advanced AD, discontinuance of oral feeding after aspiration pneumonia may be predicted by CURB-65 and MMSE scores and BMI.

Key Words: Alzheimer disease, aspiration pneumonia, CURB-65, oral feeding, pneumonia severity index

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The prevalence of Alzheimer dementia (AD) in Japanese individuals aged 65 years or above has increased significantly from 1.5% in 1985 to 7.2% in 2012.¹ Its prevalence is also increasing in the United States; AD being a leading cause of death in that country. Population-based studies have estimated that 600,000 US Americans with AD die per year.² AD, a progressive and incurable disease, leads to loss of cognitive function and subsequent death.³ Difficulties with oral feeding resulting from loss of interest in eating, or dysphagia, or both is the most commonly observed complication, occurring in 86% of patients with AD in its final stages, which can last from 6 months to 2 years.^{2,3} In addition, febrile episodes (53% of patients) and pneumonia (41% of patients) are also common in final stage AD.

Eating problems in patients with final stage AD can be classified as follows: (i) oral phase dysphagia, including chewing and tongue movement problems; (ii) pharyngeal phase dysphagia, in which food or liquid accidentally enters the airways; and (iii) inability to feed themselves or refusal to eat.³ Eating problems are crucial, being closely associated with malnutrition and aspiration pneumonia leading to death.⁴ One option for managing eating problems is feeding by a nasogastric or gastrostomy tube; however, in patients with advanced dementia there is insufficient reported evidence for benefits of tube feeding in terms of survival, quality of life, nutritional status, physical function, and prevention of aspiration.^{2,3} Rather, tube feeding is associated with a higher incidence of new pressure ulcers and may both increase the risks of complications and necessitate use of physical restraints.² Therefore, palliative care is an important possible management option for patients with AD and severe eating problems.

A previous study has shown that 41% of hospitalized Japanese patients with aspiration pneumonia do not achieve total oral intake within 30 days; predictors of delayed oral intake include underweight, high pneumonia severity scores, and presence of comorbidities.⁵ Another study has shown that severity of AD is significantly associated with swallowing dysfunction.⁶ However, the former study included patients who did not have AD and the latter did not focus on patients with aspiration pneumonia. Discontinuance of oral feeding is a crucial issue in patients with advanced AD and aspiration pneumonia. However, to our knowledge, multivariate analysis of common parameters affecting discontinuance of oral feeding, such as cognitive function test scores, status of activities of daily living, pneumonia

severity, and blood sample data, has not been sufficiently performed. Therefore, the primary objective of this study was to investigate predictors of difficulty in oral intake leading to discontinuance of oral feeding after aspiration pneumonia in patients with AD, using parameters obtained at an early stage of hospitalization.

MATERIALS AND METHODS

Patients

For this retrospective study, 60 consecutive patients with AD (34 men, 26 women) who had been admitted in Shibukawa Medical Center (Gunma, Japan) for treatment of aspiration pneumonia from April 2016 to March 2018 were identified in our hospital database. All patients had been diagnosed as having AD before admission by neurologists according to the criteria of the Diagnostic and Statistical Mental Disorders manual and diagnostic guidelines of the National Institute on Aging-Alzheimer's Association workgroups for AD.^{7,8} Diagnoses of aspiration pneumonia were made according to the Japanese Respiratory Society guidelines for management of hospital-acquired pneumonia in adults and clinical practice guidelines for nursing-associated and health care-associated pneumonia.^{9,10} First, patients who met the following 2 conditions were diagnosed as having pneumonia: (i) pulmonary alveolar infiltration on plain radiographs or computed chest tomography; and (ii) 2 of the following: fever $>37.5^{\circ}\text{C}$, high C-reactive protein concentration, and white blood cell count above $9000/\text{mm}^3$. Second, a definite diagnosis of aspiration pneumonia also required at least one of the following: (i) accidental aspiration of food or fluid into the lung before onset of pneumonia witnessed by nursing staff or; (ii) accidentally swallowed food or fluid proven by intratracheal aspiration.

None of the study patients underwent artificial ventilation or received adrenocortical steroids before and after hospitalization. All patients received rehabilitation including physical, occupational, and speech therapy. Swallowing function was evaluated from the day after hospitalization. This study was approved by the Shibukawa Medical Center Ethics Committee and written informed consent for inclusion was obtained from all enrolled patients and their family members.

Clinical Findings

Study patients were allocated to 1 of 2 groups according to oral intake status on discharge: able to eat by mouth (oral feeding group) and unable to consume food orally, leading to discontinuance of oral feeding (discontinuance group). The following data were compared between these groups: mean age, sex, level of nursing care before hospitalization (home or nursing facility), body mass index (BMI), time since diagnosis of AD, duration of hospitalization, comorbidities, and regular medications. Mini Mental State Examination (MMSE) and Functional Independence Measure (FIM) scores for assessing daily cognitive and physical ability,^{11,12} and CURB-65 and pneumonia severity index (PSI) scores to evaluate the severity of pneumonia on admission^{13,14} were compared between the groups. In addition, various investigation-related variables, including blood and biochemistry data on admission, comorbidities, medications, antibiotics administered on admission, and species of bacteria detected on sputum culture were compared between the groups.

Statistical Analysis

Continuous data are presented as mean \pm SD or n (%). Admission data were compared between the oral feeding and

discontinuance groups using the unpaired *t* test for parametric data and Mann-Whitney *U* test for nonparametric data. Nonparametric data were compared between the 2 groups using the χ^2 test. All *P*-values were 2 sided; $P < 0.05$ were considered to denote statistical significance.

Pearson correlation coefficient was used to analyze correlations between CURB-65 or PSI scores and independent variables, including BMI, time since diagnosis of AD, MMSE and FIM scores, lymphocyte count, and serum albumin (Alb), total cholesterol (T-Cho), and cholinesterase (ChE), triglyceride (TG) concentrations, hemoglobin A1c (HbA1c), and lymphocyte count; all of which differed significantly ($P < 0.05$) between the 2 groups. Multivariate stepwise linear regression analysis using the variables with correlations of $P < 0.10$ by univariate analysis was performed to investigate associations between each variable and CURB-65 or PSI. Interaction or confounding among independent variables was evaluated by addition of interaction terms consisting of the product of 2 independent variables to a regression equation that included 2 chosen independent variables.

Multivariate logistic regression analysis of the 11 above-listed independent variables that differed significantly between the 2 groups was then performed to estimate the risk of inability to take food orally after aspiration pneumonia. Before logistic regression analysis, correlations among these 11 independent variables were investigated in each group. Standard methods were used to estimate sample size for multiple logistic regression; at least 10 outcomes were needed for each included independent variable. Therefore, 3 independent variables were chosen from the above 11 variables using a round robin algorithm and a significant model showing the minimum Akaike information criterion with all variables having $P < 0.05$ was constructed. Combining 2 independent variables with an absolute value of the correlation coefficient > 0.40 was avoided; only 1 of such 2 variables was selected when choosing 3 independent variables, even if the significant correlation was observed in only 1 study group. Three methods proposed by Hosmer and Lemeshow,¹⁵ namely LOESS (locally weighted least squares) smoothing curves, design variables, and fractional polynomials, were used to determine whether the dependent variable was linear in the logit. Regarding interaction between independent variables, a logistic model that contained all covariates as possible confounders was constructed. Interaction terms (product of 2 independent variables in all combinations) were analyzed by addition of the product to the generalized additive model including 2 chosen variables. It was proven that there were no interactions between each independent variable. A variance inflation factor was used to check for multicollinearity on multivariate linear or logistic regression analysis. A variance inflation factor of > 10 indicates serious multicollinearity, whereas a value > 4 may be a cause for concern. Goodness of fit of the logistic regression model was evaluated by the area under the curve (AUC) and Hosmer-Lemeshow test. All statistical analyses were performed with EZR, a modified version of R commander (version 1.6-3) that was designed to add statistical functions frequently used in biostatistics (R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).¹⁶

RESULTS

Patients' Characteristics, Clinical Findings, and Sputum Culture Results

Relevant characteristics of the patients according to study group are shown in Table 1. Mean age, sex, place of

TABLE 1. Patients' Characteristics and Laboratory Data According to Study Group

	Discontinuance Group (n = 24)	Oral Feeding Group (n = 36)	P
Patients' characteristics			
Mean age (y)	86.8 ± 7.9	88.4 ± 8.1	0.406
Sex difference (male/female)	14/10	20/16	1.000
Patients' place of residence (patients' house/nursing home)	7/17	18/18	0.180
Hospitalization period (d)	34.0 ± 26.7	25.1 ± 18.3	0.349
Duration after diagnosis of Alzheimer disease (y)	6.5 ± 2.1	4.7 ± 1.7	0.001*
Body mass index (kg/m ²)	17.8 ± 2.1	19.5 ± 2.5	0.011*
CURB-65 score on admission	3.1 ± 0.9	2.2 ± 0.9	<0.001*
PSI score on admission	121.6 ± 18.4	107.4 ± 22.0	0.012*
MMSE score on admission	3.3 ± 3.0	9.5 ± 5.9	<0.001*
FIM score on admission	23.2 ± 9.4	37.3 ± 21.7	<0.001*
Patients' outcome at discharge (dead/alive)	9/15 (60%)	0/36 (0%)	<0.001*
Laboratory data that differed significantly between study groups			
Alb (g/dL)	2.9 ± 0.6	3.2 ± 0.4	0.047*
ChE (U/L)	155.1 ± 50.2	183.5 ± 45.7	0.013*
T-Cho (mg/dL)	140.8 ± 30.0	160.8 ± 24.8	0.017*
TG (mg/dL)	63.8 ± 15.0	81.4 ± 29.3	0.017*
HbA1c (%)	5.62 ± 0.35	5.92 ± 0.73	0.020*
Lymphocyte count (/mm ³)	641.6 ± 380.8	911.1 ± 450.5	0.019*

*Statistically significant ($P < 0.05$).
Alb indicates serum albumin; ChE, serum cholinesterase; FIM, functional independence measure; HbA1c, whole blood hemoglobin A1c; MMSE, Mini Mental State Examination; PSI, pneumonia severity index; T-Cho, serum total cholesterol; TG, serum triglyceride.

residence before admission, and duration of hospitalization did not differ significantly between these groups. However, time since diagnosis of AD (6.5 ± 2.1 vs. 4.7 ± 1.7 y, respectively; $P = 0.001$), CURB-65 score (3.1 ± 0.9 vs. 2.2 ± 0.9, respectively; $P < 0.001$), PSI score (121.6 ± 18.4 vs. 107.4 ± 22.0, respectively; $P = 0.012$), and proportion of patients who died (60% vs. 0%, respectively; $P < 0.001$) were significantly higher and the BMI (17.8 ± 2.1 vs. 19.5 ± 2.5, respectively; $P = 0.011$), MMSE score (3.3 ± 3.0 vs. 9.5 ± 5.9, respectively; $P < 0.001$), and FIM score (23.2 ± 9.4 vs. 37.3 ± 21.7, respectively; $P < 0.001$) significantly lower in the discontinuance than the oral feeding group. In addition, serum concentrations of Alb (2.9 ± 0.6 vs. 3.2 ± 0.4 g/dL, respectively; $P = 0.047$), ChE (155.1 ± 50.2 vs. 183.5 ± 45.7 U/L, respectively; $P = 0.013$), T-Cho (140.8 ± 30.0 vs. 160.8 ± 24.8 mg/dL, respectively; $P = 0.017$), TG (63.8 ± 15.0 vs. 81.4 ± 29.3 mg/dL, respectively; $P = 0.017$), blood HbA1c values (5.62% ± 0.35% vs. 5.92% ± 0.73%, respectively; $P = 0.020$), and lymphocyte count (641.6 ± 380.8 vs. 911.1 ± 450.5/mm³, respectively; $P = 0.019$)

TABLE 2. Comorbidities, Medications, Antibiotics, and Species of Bacteria in Sputum Cultures According to Study Group

	Discontinuance Group (n = 24)	Oral Feeding Group (n = 36)	P
Comorbidities			
Hypertension	9	18	0.430
Diabetes mellitus	3	6	0.729
Renal diseases	2	4	1.000
Heart diseases	2	5	0.691
Cerebrovascular diseases	2	3	1.000
Pulmonary diseases	0	0	1.000
Medications			
Antihypertensive agents			
Angiotensin-converting enzyme inhibitor	0	1	1.000
Angiotensin II receptor blocker	1	8	0.072
Calcium channel blocker	8	15	0.594
α-Blocker	0	2	0.512
Digestive medicine			
Proton pump inhibitor	7	11	1.000
H2-antagonist	3	2	0.380
Gastrointestinal prokinetic agent	3	5	1.000
Antidementia medicine			
Cholinesterase inhibitor	6	7	0.751
Memantine	0	1	1.000
Antibiotics used on admission			
Sulbactam/ampicillin	15	23	1.000
Tazobactam/piperacillin	5	3	0.247
Ceftriaxone	3	6	0.729
Meropenem	1	4	0.639
Bacteria detected in sputum cultures			
<i>Streptococcus pneumoniae</i>	3	1	0.292
<i>Klebsiella pneumoniae</i>	1	3	0.643
<i>Pseudomonas aeruginosa</i>	3	2	0.380
<i>Escherichia coli</i>	0	2	0.512
<i>Methicillin-resistant Staphylococcus aureus</i>	2	0	0.156
<i>Proteus mirabilis</i>	1	0	0.400
<i>Moraxella catarrhalis</i>	0	1	1.000
<i>Candida albicans</i>	2	2	1.000
Only indigenous bacteria	12	12	0.058

were significantly lower in the discontinuance than oral feeding group.

Comorbidities, taking of medications, antibiotics used on admission, and bacterial species detected in sputum cultures are shown in Table 2. None of these factors differed significantly between the groups.

Correlations Between CURB-65 or PSI Scores and Independent Variables on Admission

In the discontinuance group, the CURB-65 score on admission was not significantly correlated with the following independent variables: BMI, time since diagnosis of AD, MMSE score, FIM score, CURB-65 score, Alb, ChE, T-Cho,

TABLE 3. Correlations Between CURB65/PSI Scores and Independent Variables

Independent Variables	Correlation Efficient (<i>P</i>)
A. Univariate analysis of correlations between CURB-65 score and independent variables with <i>P</i> < 0.10	
Discontinuance group	
Serum ChE	−0.395 (0.056)
Oral feeding group	
FIM score	−0.413 (0.012*)
BMI	−0.341 (0.040*)
B. Univariate analysis of correlations between PSI score and independent variables with <i>P</i> < 0.10	
Discontinuance group	
Serum ChE	−0.580 (0.003*)
Serum T-Cho	−0.438 (0.032*)
BMI	−0.395 (0.056)
Oral feeding group	
FIM score	−0.496 (< 0.001*)
MMSE score	−0.421 (0.011*)
HbA1c	−0.336 (0.045*)
Age	0.295 (0.081)
C. Results of multivariate linear regression analysis	
Factors associated with CURB-65 score in the discontinuance group (regression equation having statistical significance was not obtained)	
Factors associated with CURB-65 score in the oral feeding group (<i>R</i> , 0.53; <i>R</i> ² , 0.28; adjusted <i>R</i> ² , 0.24; ANOVA <i>P</i> = 0.004*)	
Independent variables	<i>B</i> (95% CI) β <i>t</i> VIF <i>P</i>
Intercept	0.458 (−1.746 to 2.663) 0.423 0.675
FIM	−0.017 (−0.030 to −0.004) −0.405 −2.741 1.000 0.010*
BMI	0.120 (0.011-0.230) 0.331 2.243 1.000 0.032*
Factors associated with PSI score in the discontinuance group (<i>R</i> , 0.55; <i>R</i> ² , 0.34; adjusted <i>R</i> ² , 0.31; ANOVA <i>P</i> = 0.003*)	
Intercept	154.454 (10.327-133.038) 14.957 < 0.001*
Serum ChE	−0.212 (−0.344 to −0.080) −0.580 −3.339 1.000 0.003*
Factors associated with PSI score in the oral feeding group (<i>R</i> , 0.50; <i>R</i> ² , 0.25; adjusted <i>R</i> ² , 0.22; ANOVA <i>P</i> = 0.002*)	
Intercept	126.214 (112.974-139.453) 19.373 < 0.001*
FIM	−0.504 (−0.812 to −0.196) −0.496 −3.329 1.000 0.002*

ANOVA indicates analysis of variance; *B*, nonstandardized regression coefficient; β, standardized regression coefficient; BMI, body mass index; ChE, cholinesterase; FIM, functional independence measure; HbA1c, hemoglobin A1c; MMSE, mini mental state examination; *R*, multiple correlation coefficient; *R*², coefficient of determination; T-Cho; total cholesterol; VIF, variance inflation factor.

**P* < 0.05. Data are presented as correlation coefficient (*P* value).

TG, HbA1c, or lymphocyte count (Table 3A). However, in the oral feeding group the CURB-65 score on admission was significantly correlated with FIM score ($r = -0.413$; $P = 0.012$) and BMI ($r = -0.341$; $P = 0.040$) (Table 3A). Serum ChE ($r = -0.580$; $P = 0.003$) and T-Cho ($r = -0.438$; $P = 0.032$) concentrations in the discontinuance group and FIM score ($r = -0.496$; $P < 0.001$), MMSE score ($r = -0.421$; $P = 0.011$), and blood HbA1c value ($r = -0.336$; $P = 0.045$) in the oral feeding group were significantly associated with PSI score (Table 3B).

Next, multivariate regression analysis was performed based on the above findings (Table 3C). The statistical significance of associations with CURB-65 score could not be calculated in the discontinuance group, whereas, in the oral

feeding group, FIM ($\beta = -0.405$; $P = 0.010$) and BMI ($\beta = 0.331$; $P = 0.032$) were significantly correlated with CURB-65 score. PSI score was significantly correlated with a serum ChE concentration ($\beta = -0.580$; $P = 0.003$) in the discontinuance group and FIM score ($\beta = -0.496$; $P = 0.002$) in the oral feeding group.

Multivariate Logistic Regression Analysis to Determine Predictors of Discontinuance of Oral Feeding

Multivariate logistic regression analysis revealed that CURB-65 score, BMI, and MMSE score may be predictors of discontinuance of oral feeding in patients with advanced

TABLE 4. Results of Logistic Regression Analysis to Determine Independent Variables Affecting Discontinuance of Oral Feeding

	Partial Regression Coefficient	VIF	<i>P</i>	Odds Ratio	95% CI of Odds Ratio
Intercept	7.187		0.031*	1322.64	
CURB-65 score	1.748	1.867	0.004*	5.740	1.770-18.600
BMI	−0.569	1.782	0.009*	0.566	0.369-0.867
MMSE score	−0.296	1.073	0.010*	0.744	0.595-0.930

Model χ^2 test: $P < 0.001$.

Percentage of correct classifications: 81.67%.

AUC: 0.918 (95% CI, 0.852-0.984).

AIC: 49.66.

AIC indicates Akaike information criterion; AUC, area under the curve; BMI, body mass index; MMSE, mini mental state examination; VIF, variance inflation factor.

**P* < 0.05.

AD (Table 4). Specifically, CURB-65 score showed an odds ratio of >1.0 (5.740; $P=0.004$), whereas for BMI and MMSE score odds ratio was <1.0 (0.566; $P=0.009$ and 0.744; $P=0.010$, respectively); 81.67% were correctly classified and the AUC 0.918. The P -value for the Hosmer-Lemeshow goodness of fit test was 0.779, indicating no evidence of poor fit.

DISCUSSION

In a previous study of 66,661 older Japanese patients with aspiration pneumonia, 59% of them achieved total oral intake within 30 days of hospitalization.⁵ In the present study, 36 of 60 consecutive patients with AD and aspiration pneumonia (60%) who were admitted to our hospital had achieved total oral intake by discharge (oral feeding group), consistent with the previously reported data.⁵ Time since diagnosis of AD was longer and CURB-65 score, PSI score, and in-hospital mortality significantly higher in the discontinuance than the oral feeding group, whereas BMI, MMSE score, and FIM score were significantly lower in the discontinuance than the oral feeding group. On admission, Alb, ChE, T-Cho, TG, and HbA1c were significantly lower in the discontinuance than oral feeding group. Interestingly, serum Alb, ChE, and T-Cho concentrations and blood lymphocyte count are well-known indicators of nutritional status^{17,18}; thus, our findings suggest that patients were more severely malnourished in the discontinuance than the oral feeding group. Next, we focused on identifying correlations between severity of aspiration pneumonia and clinical variables that differed significantly between the discontinuance and oral feeding groups. Interestingly, multivariate stepwise linear regression analysis revealed associations between both CURB-65 and PSI scores, but not MMSE scores, with FIM scores in the oral feeding group. The FIM includes 13 items evaluating motor dysfunction (FIM motor scores) and 5 items evaluating cognitive dysfunction (FIM cognition scores).¹² FIM motor scores correlate with Barthel Index scores whereas FIM cognition scores correlate with MMSE scores¹⁹; therefore, total FIM scores (FIM motor+FIM cognition scores) reflect overall condition in patients with AD, including both physical and cognitive impairments. MMSE scores do not include evaluation of motor dysfunction. Thus, our findings suggest an association between severity of pneumonia and physical ability or activity in patients with AD who can consume food orally. A recent study revealed that impaired cortical control of swallowing leads to reduced hypolaryngeal elevation in patients with early AD.²⁰ Therefore, low FIM scores may be associated with swallowing dysfunction, contributing to increasing the severity of aspiration pneumonia. Moreover, in the oral feeding group, both FIM scores and BMI were significantly correlated with CURB-65 scores. Individuals with BMI of <20 kg/m² reportedly have a 34% greater risk of dementia than those with a healthy BMI.²¹ Interestingly, there is a correlation between high serum adiponectin concentrations, which facilitate fatty acid breakdown, and low BMI in older persons with mild dementia²²; additionally, lower BMIs are associated with cerebrospinal markers of AD in patients with mild AD.²³ Also, loss of muscle mass leading to low BMI is a potential predictor of mortality in older adults with aspiration pneumonia.²⁴ Thus, a low BMI may reflect progression of AD and therefore be a risk factor for severe aspiration pneumonia in patients with early or middle stage AD in the oral feeding group. However, neither FIM score nor BMI was associated with CURB-65 or PSI score

in the discontinuance group according to multivariate linear regression analysis. Rather, ChE concentration was negatively correlated with PSI score in that group. A previous study found significantly negative correlations between serum ChE concentration and severity of pneumonia as determined by both CURB-65 and PSI scores.²⁵ Low serum ChE concentrations denote poor nutritional status and malnutrition causes immune dysfunction²⁶; the latter may therefore be the mechanism for more severe aspiration pneumonia. In addition, low serum ChE concentrations lead to increases in serum acetylcholine concentration, which may induce immunosuppression given that acetylcholine has immunosuppressive effects on macrophages or other immune cells; this regulatory pathway mainly involves a link between neurotransmitters in blood and macrophages.²⁷ Taken together, these findings suggest that low ChE concentrations can lead to potent immunosuppression by increasing serum acetylcholine. Malnutrition also increases acetylcholine esterase activity in the cerebellum, striatum, and hypothalamus in rat models.²⁸ Another study has shown that malnutrition induces significant decreases in muscarinic receptors in the hippocampus of rats by protein-energy malnutrition.²⁹ Thus, these findings suggest that malnutrition per se may relate to progression of AD and that serum ChE concentrations are an important nutrition-related variable in patients with advanced AD.

In the present study, multivariate logistic regression analysis revealed associations between the 3 independent variables of CURB-65 score, BMI, and MMSE score and discontinuance of oral feeding in patients with AD and aspiration pneumonia. Interestingly, Momosaki et al⁵ also reported similar results: they found that delayed initiation of oral intake in patients with aspiration pneumonia is associated with being underweight and high scores for pneumonia severity. In addition, in the present study we found that CURB-65 score is also associated with discontinuance of oral feeding. The question now arises: why did CURB-65 score, not PSI score, correlate with discontinuance of oral feeding? One possible explanation is the contribution of the patients' age to CURB-65 scores: PSI scores includes the patient's age whereas CURB-65 scores only allot 1 point for patients aged 65 years or above. In the present study, patients' ages did not differ significantly between the 2 groups; thus, the fact that evaluation of severity of pneumonia did not involve age in this study may have played a key role in determining our findings. Another group of researchers attempted to improve predictability of 30-day mortality when using CURB-65 by adding items unrelated to patients' ages and found that this resulted in improved accuracy of prediction, suggesting the importance of variables other than age when evaluating pneumonia severity.³⁰ Our data also suggest that preventing worsening of aspiration pneumonia may lead to preservation of the ability to consume food orally, which relates to the importance of preventing aspiration pneumonia in nonhospitalized individuals with AD.

Interestingly, BMI and MMSE scores were also associated with discontinuance of oral feeding in our study. Weight loss is reportedly associated with rapid disease progression in patients with mild cognitive impairment; however, this association has not been shown for patients with AD.³¹ Another study reported leveling off of BMI after the onset of clinical AD.³² However, when dementia progresses, severe weight loss can become a serious problem that leads to protein-energy malnutrition³³ and decreased skeletal muscle index associated with poor swallowing function.³⁴ Consistent with this, our data suggest that a low BMI can be a predictor of impaired swallowing function in

patients with advanced dementia. Also of note, MMSE score, not FIM score, was significantly associated with discontinuance of oral feeding, which suggest that various factors other than physical disability, including swallowing dysfunction, may contribute to the discontinuance of oral feeding. For example, appetite change has been reported in nearly half of patients with mild AD and changes in eating habits and food preferences are characteristically marked in patients with moderate AD.³⁵ Certainly, swallowing disturbance is a critical problem in patients with severe AD; additionally, such patients may also be unable to feed themselves or refuse to eat.² Our findings suggest that MMSE score may reflect potential eating problems such as inability or refusal to eat resulting from cognitive dysfunction and that such eating problems may have a greater impact on discontinuance of oral feeding than has been recognized hitherto in patients with AD. The above findings indicate that difficulties with oral feeding in patients with AD and aspiration pneumonia may be determined by a combination of factors that reflect cognitive and swallowing dysfunction as well as the severity of pneumonia on admission.

Limitations

This study is limited by comprising relatively few patients from a single institution, possible selection bias, and its retrospective cross-sectional design. We mainly used univariate and multivariate regression analysis to investigate associations between independent variables and the severity of aspiration pneumonia, and multivariate logistic regression analysis to investigate associations between independent variables and discontinuance of oral feeding. Therefore, the relationships between these variables are unclear. In addition, we employed the independent variable “time since diagnosis of AD”, which is an approximation rather than a precise measure of duration of AD. We did not include data on swallowing function tests in the present study, because these tests had been performed in too few patients. Similarly, we did not have the data to evaluate parameters such as patients’ ability to follow caregivers’ instructions, alertness, cognitive fluctuations, or previous history of aspiration pneumonia, all of which may affect discontinuance of oral feeding. Concerning logistic regression analysis, we assigned only 3 independent variables to avoid overfitting and therefore we may have overlooked other independent variables that are associated with discontinuance of oral feeding; nevertheless, our analysis showed a decent percentage of correct classifications (81.67%) and AUC (0.918). Large prospective cohort studies are needed to further explore interactions and relationships between independent variables.

CONCLUSIONS

The severity of aspiration pneumonia in patients with AD was most strongly and negatively correlated with serum ChE concentrations in the discontinuance group and with the FIM score in the oral feeding group. CURB-65 score, BMI, and MMSE score were significantly associated with discontinuance of oral feeding, suggesting that simple and well-known scoring systems for severity of pneumonia and cognitive function, together with BMI, may be useful in predicting difficulty with oral feeding during hospitalization and that preventing deterioration of aspiration pneumonia may be important in preserving the ability of patients with advanced AD to consume food orally.

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REFERENCES

- Ohara T, Hata J, Yoshida D, et al. Trends in dementia prevalence, incidence, and survival rate in Japanese community. *Neurology*. 2017;88:1925–1932.
- Mitchell SL. Clinical practice. Advanced dementia. *N Engl J Med*. 2015;372:2533–2540.
- Goldberg LS, Altman KW. The role of gastrostomy replacement in advanced dementia with dysphagia: a critical review. *Clin Interv Aging*. 2014;9:1733–1739.
- Priefer BA, Robbins J. Eating changes in mild-stage Alzheimer’s disease: a pilot study. *Dysphagia*. 1997;12:212–221.
- Momosaki R, Yasunaga H, Matsui H, et al. Predictive factors for oral intake after aspiration pneumonia in older adults. *Geriatr Gerontol Int*. 2016;16:556–560.
- Sato E, Hirano H, Watanabe Y, et al. Detecting signs of dysphagia in patients with Alzheimer’s disease with oral feeding in daily life. *Geriatr Gerontol Int*. 2014;14:549–555.
- American Psychiatric Association. *Diagnostic and Statistical Manual Disorders*, 4th ed., text revision. Washington, DC: American Psychiatric Association; 2000.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement*. 2011;7:263–269.
- Committee for the Japanese Respiratory Society guidelines for management of respiratory infections. The Japanese Respiratory Society guidelines for management of hospital-acquired pneumonia. *Respirology*. 2004;9:S1–S50.
- Kohno S, Imamura Y, Shindo Y, et al. Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP) [complete translation]. *Respir Investig*. 2013;51:103–126.
- Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. *Appl Nurs Res*. 2000;13:209–213.
- Linacre JM, Heinmann JW, Wright BD, et al. The structure and stability of the functional independence measure. *Arch Phys Med Rehabil*. 1994;75:127–132.
- Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382.
- Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med*. 1997;336:243–250.
- Hosmer DW, Lemeshow SA. *Goodness of Fit for the Multiple Logistic Regression Model: Applied Logistic Regression*. New York: Wiley; 1989.
- Kanda Y. Investigation of the freely-available easy-to-use software “EZ R” (Easy R) for medical statistics. *Bone Marrow Transplant*. 2013;48:452–458.
- Schneider SM, Hebuterne X. Use of nutritional scores to predict clinical outcomes in chronic diseases. *Nut Rev*. 2000;58:31–38.
- Grandone I, Santaripa L, Alfonsi L, et al. Serum cholinesterase as indicator of parenteral nutrition efficacy in protein energy malnutrition: four case reports. *E Spen Eur J Clin Nutr Metab*. 2010;5:e6–e9.
- Tanaka N, Nakatsuka M, Ishii H, et al. Clinical utility of the functional independence measure for assessment of patients with Alzheimer’s disease and vascular dementia. *Psychogeriatrics*. 2013;13:19–205.

20. Humbert IA, McLaren DG, Kosmatka K, et al. Early deficits in cortical control of swallowing in Alzheimer's disease. *J Alzheimers Dis*. 2010;19:1185–1197.
21. Qizilbash N, Gregson J, Johnson ME, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol*. 2015;3:431–436.
22. Fujita Y, Toyomoto T, Sakoh-Goshima T, et al. Increased adiponectin is associated with cerebral white matter lesions in the elderly with cognitive impairment. *Metab Brain Dis*. 2018;33:1385–1388.
23. Mathys J, Gholamrezaee M, Henry H, et al. Decreasing body mass index is associated with cerebrospinal markers of Alzheimer's pathology in MCI and mild dementia. *Exp Gerontol*. 2017;100:45–53.
24. 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:e18–e22.
25. Akuzana N, Naitoh H. Nutritional parameters affecting severity of pneumonia and length of hospital stay in patients with pneumococcal pneumonia: a retrospective cross-sectional study. *BMC Pulm Med*. 2015;15:149.
26. Bourke CD, Berkley JA, Prendergast AJ. Immune dysfunction as a cause and consequence of malnutrition. *Trends Immunol*. 2016;37:386–398.
27. Pohanka M. Inhibitors of acetylcholinesterase and butyrylcholinesterase meet immunity. *Int J Mol Sci*. 2014;15:9809–9825.
28. Rocha JB, Emanuelli T, Pereira ME. Effects of early undernutrition on kinetic parameters of brain acetylcholinesterase from adult rats. *Acta Neurobiol Exp (Wars)*. 1993;53:431–437.
29. Viana GS, Figueiredo RM, Bruno JA. Effects of protein-energy malnutrition on muscarinic receptor density and acetylcholinesterase activity in rat brain. *Ann Nutr Metab*. 1997;41:52–59.
30. Liu JL, Xu F, Zhou H, et al. Expanded CURB-65: a new score system predicts severity of community acquired pneumonia with superior efficiency. *Sci Rep*. 2016;6:22911.
31. Besser LM, Gill DP, Monsell SE, et al. Body mass index, weight change, and clinical progression in mid cognitive impairment and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2014;28:36–43.
32. Gu Y, Scameas N, Cosentino S, et al. Change in body mass index before and after Alzheimer's disease onset. *Curr Alzheimer Res*. 2014;11:349–356.
33. Faxén-Irving G, Fereshtehnejad SM, Falahati F, et al. Body mass index in different dementia disorders: results from the Swedish Dementia Quality Registry (SveDem). *Dement Geriatr Cogn Dis Extra*. 2014;4:65–75.
34. Takagi D, Hirano H, Watanabe Y, et al. Relationship between skeletal muscle mass and swallowing function in patients with Alzheimer's disease. *Geriatr Gerontol Int*. 2017;17:402–409.
35. Kai K, Hashimoto M, Amano K, et al. Relationship between eating disturbance and dementia severity in patients with Alzheimer's disease. *PLoS One*. 2015;10:e0133666.