

Risk factors for mortality in aspiration pneumonia: a single-center retrospective observational study

Madoka Ito¹, Naoto Ishimaru¹, Toshio Shimokawa², Yoshiyuki Kizawa³

¹Department of General Internal Medicine, Akashi Medical Center, Akashi, Hyogo; ²Clinical Study Support Center, Wakayama Medical University, Wakayama City; ³Department of Palliative Medicine, Kobe University School of Medicine, Kobe, Hyogo, Japan

Correspondence: Madoka Ito MD, Akashi Medical Center, 743-33, Ohkubo-cho Yagi, Akashi, Hyogo 674-0063, Japan.
Tel. +81.78.936.1101 – Fax: +81.78.936.7456.
E-mail: ad25klj0w@hotmail.co.jp

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Informed consent: written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article. The manuscript does not contain any individual person's data in any form.

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Abstract

Aspiration pneumonia (AP) is the leading cause of death among the elderly in Japan. The factors associated with the survival of elderly patients with AP are investigated in this retrospective observational study. Patients with AP over the age of 60 who were assessed for swallowing function in our hospital between April 2015 and March 2016 were eligible. Data on patients' body mass index (BMI), food consistency, and Karnofsky performance status were collected from medical records in hospital and again after recovery. Following hospital discharge, eligible patients were sent questionnaires containing information about their physical conditions, such as body weight and the Japanese version of the functional independence measure. Respondents were divided into two groups: those who died and those who survived, and the factors associated with patient mortality were investigated. There were 19 responses from 50 eligible patients, and seven patients died. The participants' average age was 81 years (SD 9.32). There were ten male participants (52.6%, $p=1.00$), and there were no significant differences in the mortality and survival groups. The most significant finding was that BMI was significantly lower in the patients who died ($p=0.037$, Cohen's $d=1.10$). Fisher's exact tests clearly demonstrated that patients with a BMI <19.9 had a higher mortality rate ($p=0.017$). Lower BMI may be associated with increased mortality in elderly patients with a history of AP. In general practice, BMI is simple to measure and may allow for an easy assessment of the risk of AP-related mortality.

Introduction

Pneumonia is a leading cause of mortality in Japan, within which aspiration pneumonia (AP) is included. The Statistics Bureau of Japan reported that pneumonia was the fourth leading cause of mortality in Japan in 2018 (7.5%) and AP was the seventh (3.1%) [1]. In a recent Japanese study in 22 hospitals, the proportion of patients with AP among those hospitalized for pneumonia was shown to increase with age: AP accounted for 80.1% of patients with community and hospital-acquired pneumonia over 70 years of age [2]. In a multicenter retrospective study comparing AP with other types of pneumonia, patients with AP were found to be older, had lower body mass index (BMI), and had more recurrence of AP and comorbidities [3]. The four main risk factors for AP were summarized in a recent review paper: impaired swallowing, impaired consciousness, increased chance of gastric contents reaching the lungs, and impaired cough reflex [4]. Impaired swallowing could be caused by multiple sclerosis, Parkinsonism, stroke, dementia, and mechanical ventilation. Impaired consciousness could be by stroke, cardiac arrest, medications (sleeping pills, antipsychotic medications, etc.), general anesthesia, or alcohol consumption. Increased chance of gastric contents reaching the lungs could be because of

tube feeding and reflex, and impaired cough reflex could be because of medication, alcohol intake, stroke, dementia, degenerative neurologic disease, or impaired consciousness.

In a retrospective study using data from a nationwide survey of geriatric medical and nursing centers in Japan, four risk factors for AP were identified: sputum suctioning, daily oxygen therapy, feeding support dependency, and urinary catheterization [5]. Patients were classified into two groups (those with and those without episodes of AP), and data on clinical status, activities of daily living (ADL), and major illnesses were compared between the two groups.

The prognostic factors of patients with AP have not yet been adequately determined. Impaired swallowing caused by strokes [6,7] and by dementia [8] could lead to AP. In a systematic review, diseases such as strokes, Parkinson's disease (PD), and Alzheimer's disease (AD) were reported to potentially cause dysphagia, serious complications and premature mortality [9]. Studies examined mortality and related factors, but the study subjects were limited to specific diseases. Factors associated with both mortality and recurrence in patients with AP have been investigated in studies from Japan and elsewhere [10,11]. Five risk factors for one-year mortality in patients with AP were identified in a retrospective cohort study: male sex, low BMI, hypoalbuminemia, anemia, and mechanical ventilation [10]. Patients with AP and bacterial infection were recruited, but patients designated as 'do not resuscitate' (DNR, 16.2%) were excluded. Excluding patients with agreed DNR policy in Japanese community hospitals might lead to an underestimation of AP mortality. Cardiopulmonary resuscitation (CPR) preferences in one Japanese chronic care hospital were reported, and only about 16% of all patients and their family members requested CPR in case of a sudden change [12]. Three risk factors for poor prognosis in patients with community and hospital-acquired AP were identified in a prospective survey: age > 65 years, use of inotropic support, and ineffective initial therapy [11]. The study population consisted of patients with the community and hospital-acquired AP that were admitted to the respiratory intensive care unit (ICU), so most of the patients were critically ill. Prognostic factors in patients with mild to moderate AP were not evaluated, so this study may not have complete applicability to patients with common AP in community hospitals. Only a percentage of patients admitted for community-acquired pneumonia are admitted to the ICU, with one study, for example, reporting just 10% [13].

The current study evaluates the mortality and prognostic factors of patients with AP in a hospital in Japan. Factors associated with the prognosis of patients with AP aged >60 years were investigated. The prognosis of AP is influenced by complications after hospital discharge [10], and as one of the risk factors of AP is activities of daily living (ADL) [12], we considered it necessary to investigate post-discharge factors in elderly patients. We hypothesized that if patients who could intake orally had treatable factors, the prognosis of AP could be improved. Furthermore, appropriate guidance and intervention could be provided to patients with AP. The purpose of this study is to identify factors associated with post-discharge mortality in patients with AP to improve their prognosis. The study differs from previous studies in that it examines factors after the completion of pneumonia treatment.

Materials and Methods

Study design

This retrospective observational study investigates factors associated with the survival of all patients with AP in an acute care hos-

pital between April 2015 and March 2016. Hospitalized patients diagnosed with AP were enrolled. The inclusion criterion was patients listed as having AP in medical records following assessment by a clinical nurse specialized in dysphagia. Exclusion criteria were: patients under 60 years old, those that died before discharge, patients with persistent impaired consciousness (Japan coma scale (JCS) \geq 10), and patients that required mechanical ventilation or had totally impaired oral intake. This investigation was conducted in accordance with the Declaration of Helsinki of 1975. The protocol was reviewed and approved by the ethics committee of our hospital (approval number: 28-2).

Procedures

An explanation of the study, a consent form, and a questionnaire with a reply envelope were sent to the study participants in December 2016. The response was considered to be informed written consent to inclusion in the study. No reminders were sent to non-responders. There were no adequate validated questionnaires for this purpose, so an original questionnaire was made based on a literature review [14,15] and a discussion between researchers. The following items were included in the questionnaire, distributed after hospital discharge: age, sex, height, and weight, whether the patient was alive or dead (with the cause of mortality), times of subsequent hospital admissions (yes/no, and the dates of any hospitalizations), state of consciousness, food consistency, frequency of aspiration, physical activity status, a urinary catheter (yes/no), and percutaneous endoscopic gastrostomy (PEG) tube feeding (yes/no). The JCS [16] was modified for ease of patient/family comprehension. State of consciousness was investigated by the participant's eyes being mostly open, and whether they opened when stimulated (being spoken to or their body being gently shaken). Food consistency was selected from items in reference to the *Japanese Dysphagia Diet 2013* by the Japanese Society of Dysphagia Rehabilitation Dysphagia Diet Committee [17], and classification of meal consistencies used in our hospital: normal, soft, cut, mixed, and fluid food. Frequency of aspiration was selected from the following items: i) none/almost none, ii) once within several days, iii) several times per day, d) several times per one meal, and iv) every swallowing action. Multiple choice questions were prepared (no helper, modified dependence on a helper, and complete dependence on a helper) for physical activity status with reference to the Japanese version of the *Functional Independence Measure* (FIM) [18]: eating action, oral care, hand washing, makeup/shaving, bathing, changing clothes, walking, urination/defecation, moving, and using the stairs. Urinary catheters and PEG tube feeding were items added to the questionnaire because we considered them to be related to ADL, as described in a previous study [5]. After receiving the returned questionnaires, one researcher (M.I.) obtained information from medical records during the hospital stay on the patient's height, weight, body mass index (kg/m²; BMI), food consistency and Karnofsky performance status (PS) after recovery. Medical records were examined to determine the state of consciousness after recovery. In this study, the same researchers designed the questionnaire, summarized the data, and collected the information from the medical records, so participants were numbered and shielded.

Statistical analysis

To determine the factors associated with mortality after AP, participants were categorized into mortality and survival groups. We analyzed the risk factors associated with mortality from AP using numbers of age, weight, BMI, PS, and the number of readmissions

to our hospital after initial discharge. The use of a urinary catheter, PEG tube, JCS, food consistency, weight loss, and aspiration frequency were converted into two categorical variables for simplicity in analysis. Weight changes between the earliest days of hospitalization and when the questionnaire was received after discharge were divided into 'no change', 'loss', or 'gain'. Data were summarized by frequency for categorical variables and median (with range) for continuous variables. To assess differences, Fisher's exact test was used for categorical variables and the Mann-Whitney-Wilcoxon test for numerical variables. We also measured effect sizes for those variables. Analysis was conducted on complete data only. We performed a univariate analysis of factors associated with mortality, although it was not possible to perform multiple regression analysis because of a smaller-than-expected number of cases. Receiver operating characteristic (ROC) analysis was used to evaluate the effect of BMI on survival/mortality. The area under the ROC curve (with 95% confidence interval) was used to evaluate the prediction accuracy of survival/mortality by BMI. The Youden index was used to select the optimal cutoff value. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted with R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

AP was diagnosed in 301 patients including 69 patients assessed for dysphasia by a clinical nurse specialist (Figure 1). Excluded were three patients who were under 60 years old, and 17 patients who had died before discharge. One patient was both under 60 years old and had already died. Fifty survey packages were therefore sent, and we received 19 responses (response rate: 38%). Seven patients had died (37%), confirmed by the questionnaire, and AP was the cause of mortality in five of these seven patients. Patient characteristics and clinical status of participants during hospitalization are shown in Table 1. Except for one patient, all were treated in the Departments of General Internal Medicine and Respiratory Medicine; the other was treated in the Department of Neurosurgery. The mean age of all participants was 81.4 years (SD 9.32), the mean age of the mortality group was 85.6 (SD 5.53) and of survival group was 78.9 (SD 10.38; $p=0.137$). The mean BMI of all patients was 18.2 (SD 3.43, interquartile range (IQR) 15.5-20.8), 16.1 (SD 2.79, IQR 14.4-18.5) in the mortality group, and 19.5 in the survival group (SD 3.24, IQR 16.9-21.6). The most important result is that the mean BMI was sig-

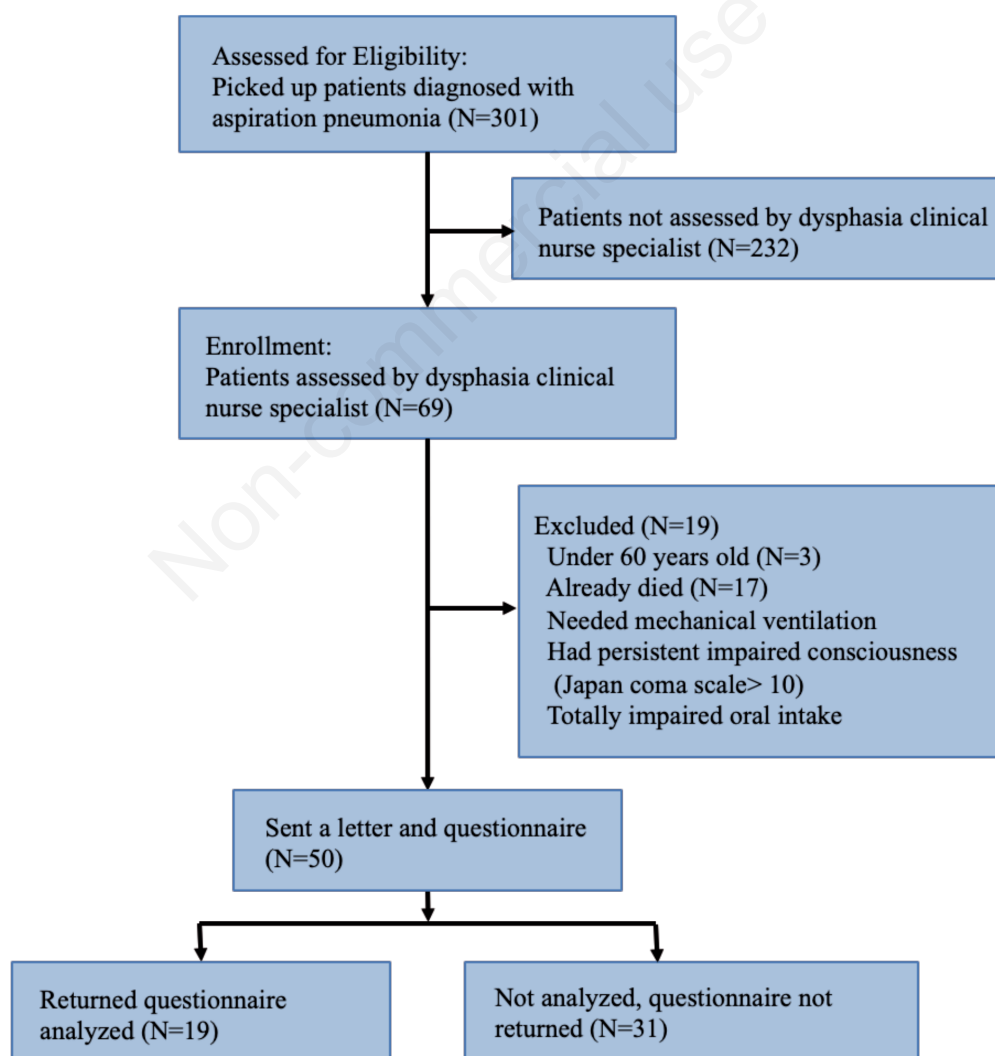


Figure 1. CONSORT diagram.

nificantly lower in the mortality group than in the survival group ($p=0.037$, Cohen's $d=1.10$). There was no difference between the groups in weight, sex, JCS, food consistency or performance status. The results of the questionnaire about life after hospital discharge are shown in Table 2. The mean number of hospitalizations for all patients was 2.6 (SD 1.98, IQR 1.5-2.5), compared with 3.3 (SD 1.98, IQR 2.0-4.0) for the mortality group and 2.2 (SD 1.95, IQR 1.0-2.0) for the survival group ($p=0.08$). Figure 2 shows the ROC curve for survival with a BMI of 19.9 as the cutoff value. The area under the ROC curve is shown as 0.798 (95% confidence interval 0.59-1.00). According to Fisher's exact tests, the mortality rate was significantly increased in patients with BMI <19.9 ($p=0.017$).

Discussion

To the best of our knowledge, this is the first study to examine factors associated with the prognosis of patients with AP from the time of hospitalization to after discharge. We followed up patients by questionnaire 9-21 months after discharge. There was a significant difference in BMI between patients in the mortality group and patients in the survival group, which is consistent with the results of previous studies. In one study, loss of muscle mass was suggested to possibly be associated with mortality after AP [19]. Poor oral health was shown to increase mortality in another study, and in another, it was suggested that patients with poor oral health may be older, under-nourished, less active, and/or have cognitive impairment [20]. Low BMI, high CURB-65 score, and low mini-mental state examination (MMSE) score were reported by Akuzawa *et al.* to be predictors of withdrawal of oral intake in patients with advanced Alzheimer's disease [21]. BMI being associated with mortality in patients with AP in our study was consistent with this. In the study by Akuzawa *et al.*, the mean BMI of the group of patients who could eat by mouth was 19.5, and that of the group of patients who could not eat was 17.8. In contrast, another study found improvements in swallowing function associated with increased BMI and muscle mass after hospitalization in an emergency hospital [22]. These results suggest that there may be a reciprocal relationship between AP and low BMI. Conversely, increased BMI and muscle mass may

improve swallowing function. AP may cause weight loss and muscle loss as sarcopenia, and in turn, this might be a trigger of further AP. Sarcopenia is a syndrome characterized by a significant loss of muscle mass and strength. It is reportedly associated not only with aging, cancer, and cognitive impairment but also with AP [23]. Sarcopenia is also associated with an increase in adverse outcomes such as falls, frailty and mortality. Management of sarcopenia is considered to be a particularly effective life extension strategy with the improvement of quality of life [24]. We, therefore, suggest that giving careful consideration to low BMI and sarcopenia may help to improve the prognosis of AP.

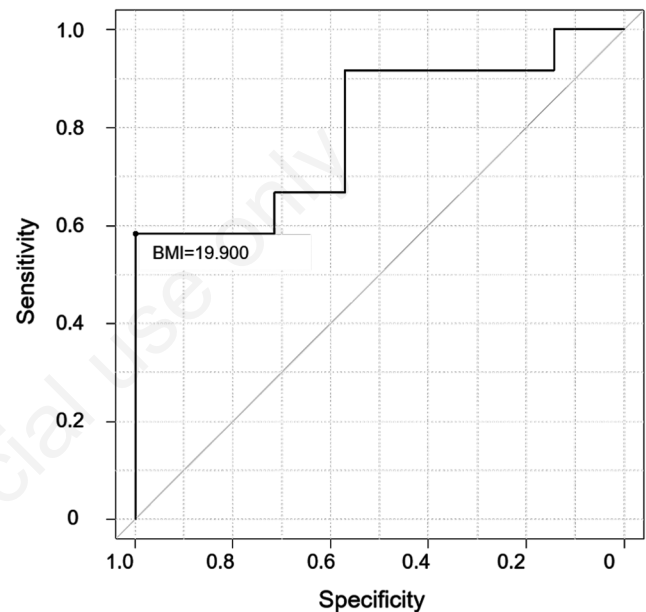


Figure 2. ROC curve of survival and BMI. Accumulation below the curve 0.798; 95% confidence interval 0.59-1.00.

Table 1. Patient Characteristics and clinical status

	Total (n=19)	Survival group (n=12)	Mortality group (n=7)	p	Effect# (95% CIs)
Age, years old, mean (SD) IQR	81.4 (9.32) 76.5-87.5	28.9 (10.38) 73.0-86.8	85.6 (5.53) 83.0-88.0	0.137	0.75 (0.22, -1.71)
Weight, mean (SD) IQR	43.4 (10.79) 33.5-49.5	45.5 (11.31) 38.3-50.3	39.5 (9.39) 33.0-44.5	0.250	0.56 (-0.39, 1.51)
BMI, mean (SD) IQR	18.2 (3.43) 15.5-20.8	19.5 (3.24) 16.9-21.6	16.1 (2.79) 14.4-18.5	0.037*	1.10 (0.10, 2.10)
Sex, male (%) Sex, female (%)	10 (52.6) 9 (47.4)	6 (50.0) 6 (50.0)	4 (57.1) 3 (57.1)	>0.99	0.07 (0.01, 0.51)
JCS I (%) JCS II over (%)	12 (63.2) 7 (36.8)	8 (66.7) 4 (34.4)	4 (57.1) 3 (57.1)	>0.99	0.10 (0.01, 0.55)
Food consistency: Normal, soft, and cut food (%) Food consistency: Mixed, and fluid food (%)	10 (52.6) 9 (47.4)	7 (58.3) 5 (41.7)	3 (42.9) 4 (57.1)	0.650	0.15 (0.11, 0.60)
PS 1 (%) PS 2 (%) PS 3 (%) PS 4 (%)	4 (21.1) 0 (0.0) 5 (26.3) 10 (52.6)	1 (5.3) 0 (0.0) 3 (15.8) 4 (21.1)	1 (5.3) 0 (0.0) 2 (10.5) 4 (21.1)	0.68	0.09 (NA, NA)

*We calculated effect sizes with Cohen's d for continuous variables and with Cramer's v for categorical variables; 95% CIs: 95% confidence intervals; IQR, interquartile range; NA, not applicable; * $p<0.05$.

Table 2. Questionnaire about life after discharge.

	Total (n=19)	Survival group (n=12)	Mortality group (n=7)	p	Effect size [#] (95% CIs)
Number of hospitalizations					
Mean (SD)	2.6 (1.98)	2.2 (1.95)	3.3 (1.98)	0.08	0.56
IQR	1.5-2.5	1.0-2.0	2.0-4.0		(0.39, -1.51)
Weight-change after discharge					
Loss or no change (%)	14 (82.4)	9 (75.0)	5 (100.0)	0.53	0.30
Gain (%)	3 (17.6)	3 (25.0)	0 (0.0)		(0.24, 0.81)
JCS I (%)	12 (70.6)	11 (91.7)	1 (20.0)	0.29	0.72
II over (%)	5 (29.4)	1 (8.3)	4 (80.0)		(0.34, 1.00)
Aspiration					
Not or almost not (%)	8 (47.1)	6 (50.0)	2 (40.0)	>0.99	0.09
More than once a day (%)	9 (52.9)	6 (50.0)	3 (60.0)		(0.24, 0.60)
Food consistency					
Normal, soft, and cut food (%)	7 (43.8)	(50.0)	1 (25.0)	0.29	0.22
Mixed, fluid food (%)	9 (56.3)	6 (50.0)	3 (75.0)		(0.25, 0.75)
Eating actions					
No helper (%)	8 (47.1)	7 (58.3)	1 (20.0)	0.18	0.43
Modified dependence (%)	6 (35.3)	4 (33.3)	2 (40.0)		(0.34, 0.92)
Complete dependence (%)	3 (17.6)	1 (8.3)	2 (40.0)		
Oral care					
No helper (%)	7 (43.8)	6 (54.5)	1 (20.0)	0.24	0.41
Modified dependence (%)	6 (37.5)	4 (36.4)	2 (40.0)		(-0.35, 0.92)
Complete dependence (%)	3 (18.8)	1 (9.1)	2 (40.0)		
Hand washing					
No helper (%)	8 (47.1)	7 (63.6)	1 (16.7)	0.20	0.47
Modified dependence (%)	6 (35.3)	3 (27.3)	3 (50.0)		(0.34, 0.96)
Complete dependence (%)	3 (17.6)	1 (9.1)	2 (33.3)		
Make-up/shaving					
No helper (%)	3 (17.6)	3 (27.3)	0 (0.0)	0.16	0.52
Modified dependence (%)	8 (47.1)	6 (54.5)	2 (33.3)		(0.34, 1.00)
Complete dependence (%)	6 (35.3)	2 (18.2)	4 (66.7)		
Bathing					
No helper (%)	2 (11.1)	2 (16.7)	0 (0.0)	0.15	0.52
Modified dependence (%)	10 (55.6)	8 (66.7)	2 (33.3)		(0.33, 1.00)
Complete dependence (%)	6 (33.3)	2 (16.7)	4 (66.7)		
Changing clothes					
No helper (%)	3 (16.7)	3 (25.0)	0 (0.0)	0.21	0.42
Modified dependence (%)	10 (55.6)	7 (58.3)	3 (50.0)		(0.33, 0.90)
Complete dependence (%)	5 (27.8)	2 (16.7)	3 (50.0)		
Walking					
No helper (%)	2 (11.1)	2 (16.7)	0 (0.0)	0.50	0.32
Modified dependence (%)	10 (55.6)	7 (58.3)	3 (50.0)		(0.33, 0.79)
Complete dependence (%)	6 (33.3)	3 (25.0)	3 (50.0)		
Urination/defecation					
No helper (%)	5 (27.8)	5 (41.7)	0 (0.0)	0.22	0.45
Modified dependence (%)	8 (44.4)	4 (33.3)	4 (66.7)		(0.33, 0.93)
Complete dependence (%)	5 (27.8)	3 (25.0)	2 (33.3)		
Urinary catheter					
Yes (%)	14 (82.4)	10 (83.3)	4 (80.0)	>0.99	0.04
No (%)	3 (17.6)	2 (16.7)	1 (20.0)		(0.24, 0.50)
Moving					
No helper (%)	6 (33.3)	6 (50.0)	0 (0.0)	0.11	0.50
Modified dependence (%)	8 (44.4)	4 (33.3)	4 (66.7)		(0.33, 0.98)
Complete dependence (%)	4 (22.2)	2 (16.7)	2 (33.3)		
Going up/down the stairs					
No helper (%)	2 (11.1)	2 (16.7)	0 (0.0)	0.65	0.30
Modified dependence (%)	7 (38.9)	5 (41.7)	2 (33.3)		(0.33, 0.77)
Complete dependence (%)	9 (50.0)	5 (41.7)	4 (66.7)		
PEG tube					
Yes (%)	2 (11.8)	1 (91.7)	1 (20.0)	0.52	0.16
No (%)	15 (88.2)	11 (8.3)	4 (80.0)		(0.24, 0.68)

[#]We calculated effect sizes with Cohen's d for continuous variables and with Cramer's v for categorical variables; 95% CIs: 95% confidence intervals; IQR, interquartile range.

This study has several limitations. It was conducted in a single hospital and the sample size was small. This may have led to reducing the generalization of our research findings, so further study with a larger sample size should be considered. Second, this study did not include all patients with AP, we only recruited patients who were able to swallow. We wanted to see changes in the post-discharge life and aspiration status of patients with AP, so we excluded patients with severe conditions who could not swallow. To examine only the relationship between prognosis and BMI, all patients with AP should be included. A third limitation is that there were various confounding factors in our study. Confounding factors were assumed for the results of the post-discharge questionnaire, such as swallowing rehabilitation, diet consistency, residential status, and other complications. Although it is difficult to eliminate these confounding factors, we suggest that they might be statistically adjusted by research with propensity score matching and sensitivity analysis. The response rate was low in this study, just 38%, so there is a potential sampling bias, and thus difficulty in generalizing the results. Participants who returned the questionnaire were likely to be more interested in AP and may have had a more severe condition. To increase the response rate, further ways to follow up could be introduced, for example by telephone or by online medical consultations. In the current study, we used an original questionnaire, so the validity and reliability have not been confirmed. Future research is thought to be needed to develop and validate a more appropriate questionnaire. The questionnaire was filled out by patients or their family members, and this may have caused some information bias depending on who filled it out. It was difficult to assign people to answer the questionnaire in the cases in which the original patient might have died or become disabled. There was also the possibility of a recall bias between the survival and mortality groups. There was potential variability in the time to mortality in this study. The time between discharge and receiving the questionnaire varied by about one year. Further research needs to be conducted in conjunction with the assessment of muscle mass and physical performance to describe the association with BMI. The results of a larger prospective study linking those markers to prognosis could lead to the development of a new strategy for future AP and BMI.

Conclusions

In conclusion, patients with AP who require hospitalization and have a low BMI may have a poor prognosis after discharge. Despite being small, the present study was still able to draw ROC curves for BMI and mortality. We believe that a large multi-center study would be able to determine the BMI values that are clearly at risk for death from AP. BMI is simple to measure in general practice and may allow for a relatively easy assessment of the risk of AP mortality.

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