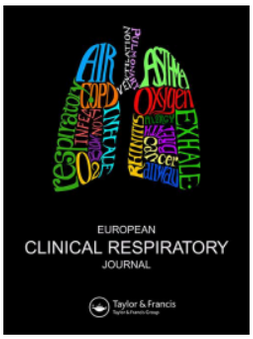

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RESEARCH ARTICLE

Investigation of predictors for in-hospital death or long-term hospitalization in community-acquired pneumonia with risk factors for aspiration

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ABSTRACT

Background: It is known that the mortality of pneumonia in patients with risk factors for aspiration is worse than that in those without these risk factors. However, it is still unknown which risk factors for aspiration predict prognosis. Therefore, we aimed to determine which risk factors for aspiration are associated with death or prolonged hospitalization.

Methods: We prospectively followed patients with community-acquired pneumonia at a single hospital providing acute to chronic care in Japan until they died or were discharged. Patients at any risk of aspiration were included. The associations between pneumonia severity, individual risk factors for aspiration, and in-hospital death or prolonged hospitalization were investigated. Overall survival was estimated by the Kaplan – Meier method, and the factors associated with in-hospital death or prolonged hospitalization were investigated by multivariate analysis using factors selected by a stepwise method.

Results: In total, 765 patients with pneumonia and risk factors for aspiration were recruited. One hundred and ten patients deceased, and 259 patients were hospitalized over 27 days. In-hospital death increased as the number of risk factors for aspiration increased. In the multivariate analysis, male, impaired consciousness, acidemia, elevated blood urea nitrogen, and bedridden status before the onset of pneumonia were associated with in-hospital death (odds ratio [OR]: 2.5, 2.5, 3.6, 3.1, and 2.6; 95% confidence interval [CI]: 1.6–4.1, 1.4–4.2, 1.6–8.0, 1.9–5.0, and 1.6–4.2 respectively). In the Cox regression analysis, these factors were also associated with in-hospital death. None of the vital signs at admission were associated. Tachycardia, elevated blood urea nitrogen, hyponatremia, and bedridden status were associated with hospitalization for >27 days (OR: 4.1, 2.3, 4.3, and 2.9; 95% CI: 1.3–12.9, 1.5–3.4, 2.0–9.4, and 2.0–4.0, respectively).

Conclusions: Blood sampling findings and bedridden status are useful for predicting in-hospital mortality and long-term hospitalization in patients with pneumonia and any risk factor for aspiration.

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KEYWORDS
Aspiration pneumonia; mortality prediction; long-term hospitalization; risk factors; blood urea nitrogen; bedridden status

Introduction

Pneumonia is a leading cause of death worldwide [1]. Specifically, aspiration pneumonia is a common bacterial pneumonia phenotype in the elderly [2]. Its incidence is reported to range from 8.5 to 66.8% among hospitalized patients with community-acquired pneumonia (CAP), depending on the definition of each study [3–7]. The mortality rate associated with aspiration pneumonia was 3.62 times higher than that of non-aspiration pneumonia [8] and may be as high as 36.8% in severe cases [9]. Patients with CAP at risk of aspiration had a 1.73 times higher risk of 1-year mortality and a 1.52 times higher risk of rehospitalization than patients without any risk factors for aspiration [10]. Most patients with aspiration pneumonia are elderly, and deterioration in activities of daily living (ADLs) due to hospitalization is usually an apprehensive problem [11]. Moreover, lowered ADLs often cause recurring aspiration pneumonia, which in turn leads to a vicious cycle of lower ADLs. Thus, aspiration pneumonia is one of the leading health-related burdens in the aging world.

Although aspiration mainly involves the inhalation of oropharyngeal or gastric contents into the lower respiratory tract, its risk factors are diverse [5,7]. The known risk factors for aspiration include neurologic

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disorders [12–14], gastric disorders [15], sedative overdose, use of hypnotics, psychotropic drug use, alcohol intoxication [16], decreased levels of consciousness [17,18], dysphagia [19], the use of nasogastric feeding tubes [20], and tracheostomy [21]. In addition, vomiting, drowning, and witnessed aspiration are the onset mechanisms of aspiration. Research on the predictors of mortality or prolonged hospitalization for aspiration pneumonia is limited because of the lack of a unified definition for aspiration pneumonia. An increased number of aspiration risk factors are reported to be associated with mortality in pneumonia cases [22], and some factors, such as altered mental status, cerebrovascular accidents, endotracheal intubation, tachycardia, and hypoxemia, were found to be associated with in-hospital death according to univariate analysis results [23].

However, despite the high mortality rates, it is still unclear which aspiration factors are associated with in-hospital death, as the risk factors for aspiration can confound each other. In the present study, we investigated the relationships between individual risk factors for aspiration, severity of pneumonia at hospitalization, and prognosis or prolonged hospitalization for the first time.

Materials and methods

Design

This was a prospective observational study involving hospitalized patients with pneumonia. The database included consecutive patients hospitalized with CAP at Ono Municipal Hospital (Ono, Hyogo, Japan) between June 2002 and December 2012. This hospital had 220 beds, provided acute care to chronic care, and discharged the patients to their home or a nursing home only when their survival was definite. The study was approved by the ethics committee of Ono Municipal Hospital (19–4(8)), and written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Patients

Hospital-admitted patients aged ≥15 years who were diagnosed with CAP were enrolled. CAP was defined as a diagnosis of pneumonia in patients living in the community, including healthcare facilities [24]. Pneumonia was diagnosed by the radiological appearance of a new and/or progressive pulmonary infiltrate(s) and at least two of the following conditions: cough, sputum or change of sputum character (increased volume and/or purulence), dyspnea, tachypnea, abnormal breathing sounds (e.g. wheezing), pleuritic chest pain, auscultatory findings on chest examination consistent with lung infiltrates, documented axillary body temperature ≥37.5°C within the past 24 h, rigors and/or chills, general malaise, and a white blood cell count ≥10,000/mm^3 or <3,000/mm^3 [5,7]. We included patients with any risk factor for aspiration [5,7]. Risk factors for aspiration are described in the Measurements section below. Patients with any of the following conditions were excluded: hospital-acquired pneumonia, immunocompromising disease or receipt of immunocompromising therapy, active lung cancer, terminal illness, pregnancy or breastfeeding, tuberculosis or fungal infection, and empyema.

Measurements

The endpoints of the study were overall survival and prolonged hospitalization. Overall survival was defined as the time from the date of admission to death for any reason. Prolonged hospitalization was defined as requiring hospital care for 28 days or more. Our hospital was a public hospital located in a rural area, and there was no hospital dedicated to chronic medical care. As such, patients were observed until death or discharged alive to their home or a nursing home only when they required no more hospitalization for additional medical treatments.

The patient background, severity items of vital signs, and the following risk factors for aspiration were screened in every patient using a checklist on the day of hospitalization: neurological disorders (acute or chronic cerebrovascular diseases), neuromuscular diseases/cerebellar degeneration/spinal cord disease, head injury, Parkinson's disease, dementia/intellectual disability, digestive tract disorders (oral/pharyngeal/throat disorder), esophageal diverticulum, achalasia/systemic sclerosis, esophageal or stomach cancer, hiatal hernia, gastroesophageal reflux disease (GERD), post-gastrectomy status (total or partial), ileus, drug-related conditions (use of sedatives/hypnotics, alcohol dependence, use of psychotropic drugs), overt aspiration, bedridden status, subjective or observed aspiration/choking/drowning or episode of vomiting before pneumonia onset, tracheostomy status, and nutrition via nasogastric tube [5,7,25]. Vital signs included body temperature, respiratory rate, systolic blood pressure, and heart rate. The laboratory data included arterial blood gas analysis, complete blood count, and biochemistry. A chest computed tomography scan was performed in all patients to determine the presence or absence of hiatal hernias and evaluate for pneumonia. GERD was defined as symptoms of gastric acid reflux or a past diagnosis of GERD and

receiving medication. Bedridden status was determined by the physician.

Pneumonia severity was assessed using the pneumonia severity index (PSI) by Fine et al. [26]. The PSI is a mortality prediction scoring system for CAP based on demographics, comorbidities, and physical and laboratory findings and is classified by weighted scores for each item. For example, 30 points are added if the pH of arterial blood is <7.35, and 10 points are added if the hematocrit is <30%. The risk of death is classified according to the total score of each item, with 90–130 points being classified as Class IV moderate-risk group and >130 points as Class V severe-risk group. The American Thoracic Society recommends the PSI to predict the prognosis and determine inpatient versus outpatient treatment locations for patients with pneumonia [27].

Statistical analysis

For background factors and baseline laboratory data, continuous variables are reported as median values and interquartile ranges. The Mann – Whitney *U* test was used to compare the medians of continuous variables (such as age), and the chi-squared test or Fisher's exact test was used to compare the proportions of categorical variables (such as sex) between the groups. Overall survival was estimated by the Kaplan – Meier method. Multivariate logistic regression analyses using stepwise methods were performed to explore factors associated with all-cause death and prolonged hospitalization. The Bayesian information criterion (BIC) was used as the criterion for variable selection in the stepwise method, selecting the model with the lowest value of the BIC to ensure a balance between goodness of fit and model complexity. We used the 38 binary variables of the PSI items and the presence or absence of risk factors for aspiration as candidate factors. Risk factors for aspiration with a frequency of less than 5% were excluded from predictors in the analysis. Pneumonia severity items were not excluded because they may be associated with death and length of hospital stay. In addition, for overall survival, Cox regression analyses were performed using factors selected by the stepwise method. Data with missing values, such as arterial blood gas analysis measurements, were excluded from the analysis. Sample size design was conducted with the number of variables set at 22, assuming that risk factors with a frequency of less than 5% were excluded, and the mortality rate for aspiration pneumonia was set at 29% based on previous reports [9,28], with a total of 750 cases set as the required number of cases. All statistical analyses were conducted using JMP version 17.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Among the 1,162 hospitalized patients with CAP, 765 (65.8%) had at least one risk factor for aspiration. The characteristics of the patients are shown in Table 1. Among the 765 patients, 413 (54.0%) were male. A total of 220 (28.8%) patients were from nursing facilities. The median PSI score was 107, with 50.6% of patients belonging to Class IV. The rate of in-hospital death was 14.2%, and the rate of prolonged hospitalization was 36.8%. Data were missing for arterial blood gas analysis in 47, blood urea nitrogen (BUN) in 2, sodium in 1, and glucose in 5 patients.

Risk factors for aspiration

The prevalence of each risk factor for aspiration is shown in Table 2. Dementia or intellectual disability

Table 1. Characteristics of the 765 patients with pneumonia and aspiration risk.

Characteristics	Patients with aspiration risk ($n = 765$)
Basal status	
Age (years)	84 (77, 89)
Male sex; n (%)	413 (54.0)
Nursing facility residence; n (%)	220 (28.8)
Physical assessment	
Impaired consciousness; n (%)	117 (15.3)
Vital signs	
Respiratory rate ≥ 30/min; n (%)	95 (12.4)
Systolic blood pressure <90 mmHg; n (%)	39 (5.1)
Body temperature < 35°C or ≥ 40°C; n (%)	10 (1.3)
Heart rate ≥ 125/min; n (%)	19 (2.5)
Examinations	
pH < 7.35; n (%)	34/718 (4.7)
PaO_2 <60 Torr; n (%)	222/718 (30.1)
BUN (mg/dL) ≥ 30 mg/dL; n (%)	169/763 (22.1)
Na (mEq/L) < 130 mEq/L; n (%)	41/764 (5.4)
Glu ≥250 mg/dL; n (%)	41/760 (5.4)
Ht < 30%; n (%)	114 (14.9)
Pleural effusion; n (%)	231 (30.2)
PSI score	107 (88, 125.5)
PSI class	
Class I; n (%)	9 (1.1)
Class II; n (%)	50 (6.5)
Class III; n (%)	158 (20.7)
Class IV; n (%)	387 (50.6)
Class V; n (%)	161 (21.0)
Death within hospital; n (%)	110 (14.2)
Duration of hospitalization	20 (14, 35)
≥28 days; n (%)	259 (33.9)

BUN, blood urea nitrogen; Glu, glucose; NA, sodium; Ht, hematocrit; Na, sodium; PaO_2, arterial O_2 pressure; PSI, pneumonia severity index.

pH and PaO_2 were analyzed using arterial blood gas samples, and BUN, Na, Glu, and Ht were analyzed using venous blood samples. The presence of pleural effusion was evaluated by chest radiography. Continuous variables are reported as median values and interquartile ranges. Items with missing values are indicated as positive number/total number.

Table 2. Prevalence of risk factors for aspiration.

Risk factors	*n* = 765
Neurological disorders	
Acute cerebrovascular disease; n (%)	10 (1.3)
Chronic cerebrovascular disease; n (%)	262 (34.2)
Neuromuscular diseases/cerebellar degeneration/spinal cord disease; n (%)	10 (1.3)
Head injury; n (%)	2 (0.3)
Parkinson's disease; n (%)	34 (4.4)
Dementia/intellectual disability; n (%)	285 (37.3)
Digestive tract disorders	
Oral/pharyngeal/throat disorder; n (%)	46 (6.0)
Esophageal diverticulum; n (%)	7 (0.9)
Achalasia/systemic sclerosis; n (%)	3 (0.4)
Esophageal or stomach cancer; n (%)	7 (0.9)
Hiatal hernia; n (%)	101 (13.2)
GERD; n (%)	73 (9.5)
Post-gastrectomy; n (%)	117 (15.3)
Ileus; n (%)	2 (0.3)
Drug-related factors	
Sedative/hypnotic use; n (%)	143 (18.7)
Alcohol dependence; n (%)	3 (0.4)
Psychotropic drug use; n (%)	6 (0.8)
Others	
Overt aspiration; n (%)	252 (32.9)
Bedridden status; n (%)	275 (35.9)
Observed aspiration/choking/drowning before pneumonia onset; n (%)	11 (1.4)
Episode of vomiting; n (%)	54 (7.1)
Tracheostomy status; n (%)	1 (0.1)
Nasogastric tube feeding status; n (%)	8 (1.0)

GERD, gastroesophageal reflux disease.

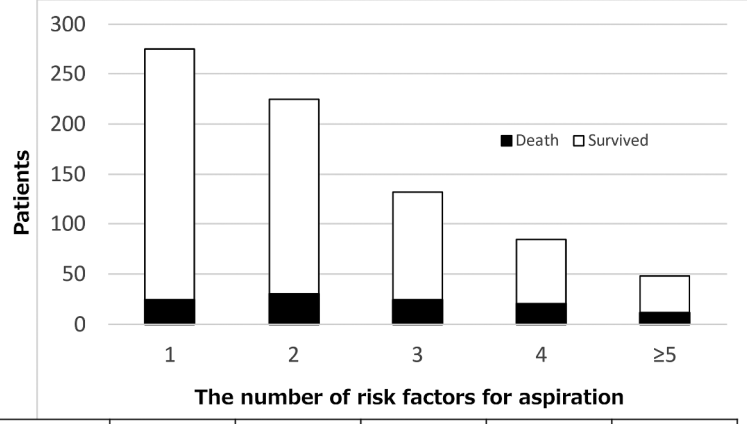
was the most common risk factor (37.3%), and factors such as chronic cerebrovascular disease, bedridden status, and overt aspiration were also observed in more than 30% of patients. Figure 1 shows the relationship between the number of risk factors and in-hospital death. Among patients with aspiration risk, 490 (64.0%) had more than one risk factor. The rate of in-hospital death in patients with more than one risk factor (86 of 490, 17.6%) was higher than that in patients with one risk factor (24 of 275, 8.7%) ($p < 0.01$), suggesting that a higher number of factors, up to five, indicates a higher in-hospital death rate.

Overall survival in patients with pneumonia and risk factors for aspiration

The median follow-up period for patients in the analysis was 153 days. In this study, the maximum follow-up period (length of hospital stay) was 200 days, and patients who were hospitalized for longer than 200 days were censored at 200 days. The total number of deaths was 110. The number of censored patients was 655, all of whom were discharged owing to cure or symptom resolution (Figure 2).

The comparison of patient characteristics in survivors and non-survivors is shown in Table 3. Excluding patients with missing values, 716 patients were included in the multivariate analysis. Multivariate logistic regression analysis with stepwise methods revealed male (odds ratio [OR]: 2.5, 95% confidence interval [CI]: 1.6–4.1), impaired consciousness (OR: 2.5, 95% CI: 1.5–4.3), acidemia (OR: 3.6, 95% CI: 1.6–8.1), elevated BUN (OR: 3.1, 95% CI: 1.9–5.0), and bedridden status (OR: 4.4, 95% CI: 2.7–7.0) as predictors for death from any cause (Table 4).

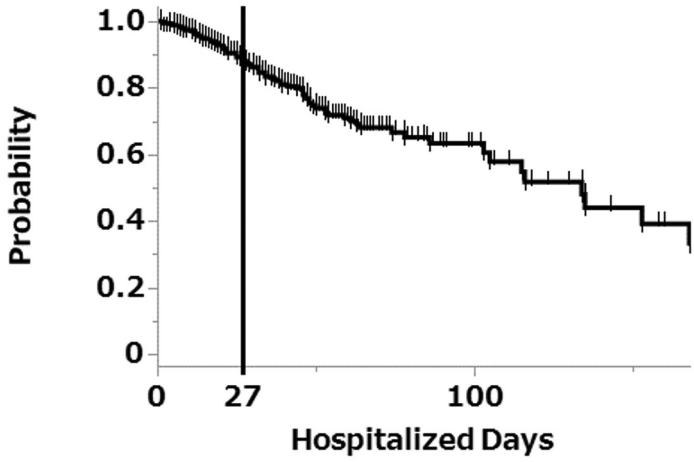
Furthermore, a Cox regression analysis using these variables showed that male (hazard ratio [HR]: 2.2, 95% CI: 1.4–3.3), conscious state (HR: 2.2, 95% CI: 1.5–3.5), acidemia (HR: 2.0, 95% CI: 1.1–3.6), elevated BUN (HR: 2.0, 95% CI: 1.4–3.0), and bedridden state (HR: 2.5, 95% CI: 1.6–3.8) in particular were associated with HRs greater than 2.0 (Table 5).



Dead/Total	24/275	30/225	24/132	20/85	12/48
Mortality (%)	8.7	13.3	18.2	23.5	25.0

Figure 1. Relationship between the number of risk factors for aspiration and patients who survived or died.

The black bars indicate patients who died during hospitalization. The white bars indicate patients who survived and were discharged alive.



Days	14	27	56	100	150	Final
Death	36	63	94	101	107	110
Censored	141	427	580	638	649	655
Number at risk	588	275	91	26	9	0

Figure 2. The Kaplan – Meier survival curve for patients with pneumonia and risk factors for aspiration. Censoring is indicated by the black mark. There were 63 deaths before the 28th day of admission.

Table 3. Association between in-hospital death and patient characteristics.

Characteristics	Survivors ($n = 655$)	Non-survivors ($n = 110$)	p-value
Basal status			
Age (years)	83 (76, 89)	85 (81, 90.3)	0.001
Male sex; n (%)	342 (52.2)	71 (64.6)	0.016
Nursing facility residence; n (%)	174 (26.6)	46 (41.8)	0.001
Physical assessment			
Impaired consciousness; n (%)	83 (12.7)	34 (30.9)	<0.0001
Vital signs			
Respiratory rate ≥ 30/min; n (%)	71 (10.8)	24 (21.8)	0.001
Systolic blood pressure <90 mmHg; n (%)	28 (4.3)	11 (10.0)	0.012
Body temperature < 35°C or ≥ 40°C; n (%)	9 (1.4)	1 (0.9)	>0.999
Heart rate ≥ 125/min; n (%)	13 (2.0)	6 (5.5)	0.031
Examinations			
pH < 7.35; n (%)	20/614 (3.3)	14/104 (13.4)	<0.0001
PaO_2 <60 mmHg; n (%)	180/614 (29.3)	42/104 (40.4)	0.024
BUN ≥30 mg/dL; n (%)	118/650 (18.1)	51 (46.4)	<0.0001
Na < 130 mEq/L; n (%)	29/654 (4.4)	12 (10.9)	0.005
Glu ≥250 mg/dL; n (%)	37/650 (5.7)	4 (3.6)	0.496
Ht < 30%; n (%)	90 (13.7)	24 (21.8)	0.028
Pleural effusion; n (%)	183 (27.9)	48 (43.6)	0.001
Risk factors for aspiration pneumonia			
Chronic cerebrovascular diseases; n (%)	211 (32.2)	51 (46.4)	0.004
Dementia/intellectual disability; n (%)	235 (35.9)	50 (45.5)	0.055
Oral/pharyngeal/throat disorder; n (%)	40 (6.1)	6 (5.5)	0.790
Hiatal hernia; n (%)	68 (10.4)	5 (4.6)	0.054
GERD; n (%)	89 (13.6)	12 (10.9)	0.443
Post-gastrectomy; n (%)	105 (16.0)	12 (10.9)	0.167
Sedative/hypnotics; n (%)	122 (18.6)	21 (19.1)	0.908
Overt aspiration; n (%)	207 (31.6)	45 (40.9)	0.055
Bedridden status; n (%)	203 (31.0)	72 (65.5)	<0.0001
Episode of vomiting; n (%)	44 (6.7)	10 (9.1)	0.369

PaO_2, arterial O_2 pressure; BUN, blood urea nitrogen; Na, sodium; Glu, glucose; Ht, hematocrit; GERD, gastroesophageal reflux disease. pH and PaO_2 were analyzed using arterial blood gas samples, and BUN, Na, Glu, and Ht were analyzed using venous blood samples. The presence of pleural effusion was evaluated by chest radiography. Age is reported as the median with the interquartile range. Items with missing values are indicated as positive number/total number.

Table 4. Predictors for in-hospital death in patients with pneumonia and risk factors for aspiration by logistic regression analysis.

Characteristics	OR	95% CI	p-value
Male sex	2.51	(1.56, 4.09)	0.0002
Impaired consciousness	2.49	(1.44, 4.25)	0.0009
pH < 7.35	3.56	(1.58, 8.06)	0.0023
BUN ≥30 mg/dL	3.09	(1.92, 4.96)	<0.0001
Bedridden status	4.35	(2.70, 7.00)	<0.0001

OR odds ratio; CI, confidence interval; BUN, blood urea nitrogen. Explanatory variables were selected by the stepwise method.

Table 5. Predictors for in-hospital death in patients with pneumonia and risk for aspiration by cox regression analysis.

Characteristics	HR	95% CI	p-value
Male sex	2.15	(1.42, 3.25)	0.0003
Impaired consciousness	2.24	(1.45, 3.45)	0.0003
pH < 7.35	2.00	(1.11, 3.60)	0.022
BUN ≥30 mg/dL	2.03	(1.36, 3.03)	0.0005
Bedridden status	2.49	(1.64, 3.76)	<0.0001

HR, hazard ratio; CI, confidence interval; BUN, blood urea nitrogen. Explanatory variables were selected by the stepwise method.

Prolonged hospitalization in patients with pneumonia and aspiration risk

According to Figure 2, 63 patients died before 27 days after admission, and these patients were excluded from the analysis of prolonged hospitalization; hence, only the patients who survived for at least 27 days after admission were included in the analysis. The comparison of patient characteristics between short-term and prolonged hospitalization is shown in Table 6. Excluding patients with missing values, 699 patients were included in the multivariate analysis. Multivariate logistic regression analysis with stepwise methods revealed tachycardia (OR: 4.1, 95% CI: 1.3–12.9), elevated BUN level (OR: 2.3, 95% CI: 1.5–3.4), hyponatremia (OR: 4.3, 95% CI: 2.0–9.4), and bedridden status (OR 2.9: 95% CI: 2.0–4.0) as predictors for prolonged hospitalization with ORs > 2.0 (Table 7).

Discussion

The prognostic scoring systems for CAP include vital signs, such as blood pressure, respiratory status, and body temperature, which are considered important for prognosis [26,29]. However, in this study, we found that in-hospital death in patients with pneumonia at risk for aspiration was significantly associated with impaired consciousness, elevated BUN level, and bedridden status. Notably, no significant association was

Table 6. Association between prolonged hospitalization and patient characteristics.

Characteristics	Short-term (n = 443)	Prolonged (n = 259)	p-value
Basal status			
Age (years)	82 (74, 88)	85 (78, 89)	0.006
Male sex; n (%)	239 (53.4)	136 (52.5)	0.712
Nursing facility residence; n (%)	104 (23.5)	92 (35.5)	0.001
Physical assessment			
Impaired consciousness; n (%)	47 (10.6)	46 (17.8)	0.07
Vital signs			
Respiratory rate ≥ 30/min; n (%)	40 (9.0)	43 (16.6)	0.003
Systolic blood pressure <90 mmHg; n (%)	17 (3.8)	14 (5.4)	0.329
Body temperature < 35°C or ≥ 40°C; n (%)	7 (1.6)	3 (1.2)	0.752
Heart rate ≥ 125/min; n (%)	5 (1.1)	9 (3.5)	0.047
Examinations			
pH < 7.35; n (%)	12/411 (2.9)	11/246 (4.5)	0.294
PaO_2 <60 mmHg; n (%)	106/411 (25.8)	90/246 (36.6)	0.003
BUN ≥30 mg/dL; n (%)	65/443 (14.7)	75/257 (29.2)	<0.0001
Na < 130 mEq/L; n (%)	10 (2.3)	23/258 (8.9)	<0.0001
Glu ≥250 mg/dL; n (%)	15/441 (3.4)	22/256 (8.6)	0.003
Ht < 30%; n (%)	59 (13.3)	38 (14.7)	0.616
Pleural effusion; n (%)	112 (25.3)	91 (35.1)	0.006
Risk factors for aspiration			
Chronic cerebrovascular diseases; n (%)	136 (30.7)	101 (39.0)	0.025
Dementia/intellectual disability; n (%)	146 (33.0)	108 (41.7)	0.020
Oral/pharyngeal/throat disorder; n (%)	29 (6.6)	12 (4.6)	0.297
Hiatal hernia; n (%)	54 (12.2)	17 (6.6)	0.017
GERD; n (%)	63 (14.2)	29(11.2)	0.252
Post-gastrectomy; n (%)	81 (18.3)	29 (11.2)	0.013
Sedative/hypnotics; n (%)	83 (18.7)	45 (17.4)	0.652
Overt aspiration; n (%)	131 (29.6)	100 (38.6)	0.014
Bedridden status; n (%)	107 (24.2)	127 (49.0)	<0.0001
Episode of vomiting; n (%)	27 (6.1)	21 (8.1)	0.308

PaO_2, partial pressure of oxygen; BUN, blood urea nitrogen; Na, sodium; Glu, glucose; Ht, hematocrit; GERD, gastroesophageal reflux disease. pH and PaO_2 were analyzed using arterial blood gas samples, and BUN, Na, Glu, and Ht were analyzed using venous blood samples. The presence of pleural effusion was evaluated by chest radiography. Age is reported as the median with the interquartile range. Items with missing values are shown as positive number/total number.

Table 7. Predictors for prolonged hospitalization in patients with pneumonia and risk factors for aspiration by logistic regression analysis.

Characteristics	OR	95% CI	p-value
Heart rate ≥ 125/min	4.07	(1.28, 12.87)	0.017
BUN ≥30 mg/dL	2.29	(1.54, 3.39)	<0.0001
Na < 130 mEq/L	4.29	(1.95, 9.41)	0.0003
Bedridden status	2.86	(2.04, 4.01)	<0.0001

OR odds ratio; CI, confidence interval; BUN, blood urea nitrogen; Na, sodium. Explanatory variables were selected by the stepwise method.

observed with any vital signs at admission. Moreover, prolonged hospitalization was significantly associated with tachycardia, elevated BUN, hyponatremia, and bedridden status; however, no significant associations were found with any respiratory condition.

The world is aging, and the incidence rates of certain diseases are changing. Aspiration pneumonia is one of the most common types of pneumonia in elderly patients with impaired swallowing function [30]. Its fatality rate is more than two times higher than that of other types of CAP [8,31]; however, studies on its prognostic factors are limited because of the small number of cases available for statistical analysis [23,32], even though interaction has been observed among the risk factors for aspiration [22]. We addressed this by conducting a cohort study consistently for over 10 years, analyzing one of the largest patient numbers ever studied in aspiration pneumonia [8], and examining the independent risk factors for the first time. In addition, hospitalization lowers the ADLs of elderly patients [11] and induces a vicious cycle of repeated aspiration pneumonia [10]. The relapse of aspiration pneumonia during hospitalization is a common problem in clinical practice. Therefore, we attempted to determine the predictors of death or prolonged hospitalization in patients with aspiration pneumonia.

No consensus regarding the definition of aspiration pneumonia exists, and the diagnosis of aspiration pneumonia has been based on multiple aspects, such as characteristic clinical history, risk factors for aspiration, or evidence of gravity-dependent opacity on chest radiography [33]. A previous report showed that patients with risk factors for aspiration had a higher mortality rate than patients without risk factors [10]. Because it is difficult to clearly diagnose a patient at risk for aspiration as aspiration pneumonia when he or she develops pneumonia, we reviewed a wide range of pneumonia that occurred in patients at risk for aspiration. To our knowledge, this is the first study to examine the relationship between each risk factor for aspiration and in-hospital death or long-term hospitalization.

First, we confirmed that in-hospital death in patients with pneumonia at risk for aspiration increased when the number of risk factors for aspiration increased (Figure 1). Even though the definitions of the risk factors differed, it was previously reported that an increasing number of risk factors is associated with higher mortality [22]. However, each risk factor can be a confounder, and it is unclear whether different risk factors can be assessed equally. Therefore, we consequently examined which risk factors are important in predicting prognosis in the present study. As a result, bedridden status was one of the most important predictors of in-hospital death or long-term hospitalization. This is consistent with our previous reports examining prognostic factors for CAP in the elderly [34].

In our study, vital signs at hospitalization were not associated with in-hospital death in the multivariate analysis. This indicates that it is difficult to distinguish between patients with aspiration pneumonia with poor or non-poor prognosis by focusing on vital signs. This may be because most patients with risk for aspiration are elderly, and their presentation of lower respiratory infections is often not prominent [35,36]. The second possibility may be that there are many cases of death along with recurring aspiration during hospitalization in patients with aspiration pneumonia, even if their vital signs are not significantly compromised at the time of admission. This hypothesis is supported by a previous study that reported that 42.5% of patients with aspiration pneumonia experienced aspiration pneumonia recurrence within 30 days, while the frequency in patients with non-aspiration pneumonia was 7.0% [37]. Another explanation could be a delayed inflammatory reaction after aspiration. These reasons might explain why existing severity scores, namely the PSI, CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, Age ≥ 65), and A-DROP (Age, Dehydration, Respiratory failure, Orientation disturbance, low blood Pressure), cannot accurately predict mortality in elderly pneumonia patients [24,34]. Since most patients at risk for aspiration are elderly, and both survivors and deceased patients are elderly, such scoring systems, which are composed of age and vital signs, are not a good predictor of prognosis for the elderly population. Thus, to properly diagnose a patient's risk of death, to decide who to admit to the hospital with limited medical resources, and to make the right decision about whether to escalate or de-escalate treatment, a new scoring system suitable for these populations is needed in the coming aging society.

In terms of prolonged hospitalization, tachycardia, elevated BUN, hyponatremia, and bedridden status were associated with hospitalization for ≥28 days in this study, while respiratory status at admission was not associated. Bedridden patients already have a decline in ADLs, and preventing the recurrence of aspiration through rehabilitation and nursing care may be more difficult than addressing other factors. Tachycardia, elevated BUN, and hyponatremia suggest dehydration or deficient intake. Although fluid replacement can improve dehydration, it does not address the patient's difficulty with intake. It was reported that hydration on admission is negatively associated with the resumption of oral intake within 30 days after aspiration pneumonia [38], and continued fluid replacement may be associated with prolonged hospitalization. Japan has a well-developed universal health insurance system, which allows for the provision of medical care for the elderly that would not be viable in other countries, making this study possible. However, how to care for such patients who require prolonged medical resources is an issue that needs to be considered by society as a whole in terms of medical economics.

The present study had several limitations. First, this was a single-center study. The background characteristics of patients with aspiration pneumonia can differ among facilities, which may affect the relative importance of the risk factors for in-hospital death or prolonged hospitalization. Thus, multicenter studies are required to confirm these findings. Second, the present study focused on several risk factors as candidates for factors associated with all-cause death and prolonged hospitalization. However, there may be other risk factors not examined in this study that require further study. In addition, this study used a stepwise method to search for factors that are important for predicting outcomes. However, there are concerns that stepwise methods may fit the data too well and lack reproducibility which may introduce bias in parameter estimation. Therefore, further study is needed to determine if the results of this study are generalizable. Third, 6.5% of cases had missing values, mainly for arterial blood gas analysis. Given that arterial blood gas analysis is not performed in all cases of pneumonia, this deficiency is not likely to be large, however, it could affect the results. However, we always perform blood gas analysis in critical cases, and we believe that the influence of the missing values on the results is minimal.

In conclusion, we found that objective data that can be obtained only through blood sampling, impaired consciousness, and bedridden status were associated with in-hospital death in patients with pneumonia at risk of aspiration, whereas vital signs at hospitalization were not important predictors. Tachycardia, elevated BUN, hyponatremia at admission, and bedridden status before pneumonia were associated with prolonged hospitalization, whereas respiratory status at admission was not.

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