

Factors Associated with Pneumonia-caused Death in Older Adults with Autopsy-confirmed Dementia

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Abstract

Objective A better understanding of risk factors for pneumonia-caused death may help to improve the clinical management of dementia.

Methods A retrospective observational study was conducted by reviewing the medical charts and autopsy reports of 204 patients who were admitted to hospital, underwent a post-mortem examination, and who were neuropathologically diagnosed with dementia. The risk factors for pneumonia-caused death were examined both as underlying and immediate causes of death using logistic regression models.

Results A high frequency of pneumonia-caused death was observed both in underlying- (37.3%) and immediate- (44.1%) cause of death, but varied according to the subtypes of dementia. The factors related to pneumonia-caused death (underlying) were subtypes of dementia; Alzheimer's disease (odds ratio [OR], 2.891; 95% confidence interval [CI], 1.459-5.730); argyrophilic grain disease (OR, 3.148; 95% CI, 0.937-10.577); and progressive supranuclear palsy (OR, 34.921; 95% CI, 3.826-318.775), dysphagia (OR, 2.045; 95% CI, 1.047-3.994), diabetes mellitus (OR, 3.084; 95% CI, 1.180-8.061) and conversely related with heart failure (OR, 0.149; 95% CI, 0.026-0.861). Factors relating to pneumonia-caused death (immediate) were incidence of pneumonia during hospitalizations (OR, 32.579; 95%CI, 4.308-246.370), gender-male (OR, 2.060; 95% CI, 1.098-3.864), and conversely related with malignant neoplasm (OR, 0.220; 95% CI, 0.058-0.840).

Conclusion The different factors relating to the pneumonia-caused death were evaluated depending on whether pneumonia was the underlying- or immediate-cause of death. Strengthening clinical management on dysphagia and diabetes mellitus, and preventing incidence of pneumonia during hospitalization appear to be the important for the terminal stage of hospitalized patients with dementia.

Key words: pneumonia-caused death, dementia, dysphagia, pneumonia, Alzheimer's disease, dementia with Lewy bodies

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Introduction

Dementia is increasingly becoming a major healthcare challenge as the population ages (1). The World Health Organization (WHO) currently estimates that 47.5 million people are living with dementia worldwide; the number is pre-

dicted to increase to 75.6 million by 2030 (2).

Pneumonia is one of the major frightened infectious diseases which associate to mortality and morbidity in older adults (3). Several studies have reported on the association between dementia and pneumonia (4-6). A meta-analysis indicated that the odds of pneumonia-caused death increased more than two fold in patients with dementia in comparison

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to those without dementia (7). An understanding of the factors associated with pneumonia-caused death in patients with dementia may help to improve clinical management; however, these factors have not been fully elucidated. Dementia covers a wide range of symptoms and encompasses a group of related neurodegenerative disorders. Many of the factors that are associated with pneumonia-caused death are likely to co-exist. In addition, the frequency of pneumonia-caused death in older adults with dementia varies and ranges from 12% (4-6) to 70% (8-14). Although a number of reasons might be responsible for these differences, one possible reason may lie in the heterogeneity of the studies, including the cause of death (underlying or immediate), the method used to obtain the cause of death (autopsy or death certificate), and the subtypes and severity of dementia (7). It was thought that the risk factors for pneumonia-caused death in older adults with dementia would also differ according to the cause of death, how the information was obtained, and the subtypes of dementia.

The aim of the present study was to evaluate the factors associated with pneumonia-caused death (both as the underlying and immediate cause of death) in older adults with autopsy-confirmed dementia and to investigate how the subtypes of dementia affect pneumonia-caused death. It is hoped that the results would contribute to the efficient clinical management of patients with dementia.

Materials and Methods

Study design and subjects

We conducted a retrospective observational study of 204 patients with dementia and neurodegenerative disorders who were hospitalized and underwent autopsy in a hospital in Toyohashi, Japan between 2005 and 2014. Some of the data that are presented in this study were obtained from our previous study, which reported on the differentiation of the prognoses of Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and vascular dementia (VaD) (9). In the present study, we collected additional data from all of the eligible patients during the observational period, regardless of the dementia subtype. Information on the general and clinical backgrounds of the patients, comorbidities and the results of neuropathological examinations were collected.

The patients were divided into 4 groups depending on the cause of death: patients who died due to pneumonia, which was the underlying cause of death "pneumonia-caused death (underlying)"; patients who died due to another condition, which was the underlying cause of death "non-pneumonia-caused death (underlying)"; patients who died due to pneumonia, which was the immediate cause of death "pneumonia-caused death (immediate); and patients who died due to another condition, which was the immediate cause of death "non-pneumonia-caused death (immediate)." Comparisons were made between the pneumonia-caused death (underlying) and non-pneumonia-caused death (under-

lying) groups, and between the pneumonia-caused death (immediate) and non-pneumonia-caused death (immediate) groups.

This study was approved by the Institutional Review Board of the University of Tsukuba and the Choju Medical Institute at Fukushima Hospital. Written informed consent was obtained from the patients' relatives.

Diagnosis and definitions

The details of the neuropathological diagnosis of each subtype of dementia and the determination of the cause of death were described in our previous study (9).

The underlying cause of death is defined as the disease, injury, or corresponding circumstance that initiated the chain of events (i.e. the intermediate cause of death) ultimately leading to death (11). The immediate cause of death is defined as the final disease, injury, or complication directly causing death (11). Dysphagia, including swallowing dysfunction, was clinically diagnosed during the hospitalization period by physicians who were specialists in geriatric medicine. The complication of pneumonia has been defined as the development of pneumonia on one or more occasions during hospitalization based on the diagnostic criteria of the Guideline for the management of hospital-acquired pneumonia in adults by the Japanese Respiratory Society (15).

Statistical analysis

The categorical variables were reported as percentages, and the continuous variables were presented as the median and interquartile range (IQR; 25-75%) or as the mean and standard deviation (SD). The characteristics of the patients who died due to pneumonia vs. those who died due to other than pneumonia were compared using the χ^2 test or Fisher's exact test (categorical variables) and the Mann-Whitney *U* test or Kruskal-Wallis test (continuous variables). The frequency of pneumonia-caused death (underlying) and pneumonia-caused death (immediate) was compared using the McNemar test. The factors associated with pneumonia-caused death were determined using logistic regression models with independent variables. A step-wise selection method was used to select variables, which were performed by the forced entry method.

The data analyses were performed using the SPSS Statistics (version 22.0, IBM, Armonk, NY, USA). In all of the analyses, the significance levels were two tailed, and *p* values of <0.05 were considered statistical significance.

Results

Characteristics of the patients who died due to pneumonia vs. non-pneumonia as underlying and immediate causes

In the grouping of underlying cause of death, 76 (37.3%) were assigned to the pneumonia-caused death (underlying) group and 128 (62.7%) to the non-pneumonia-caused death

Table 1. Characteristics of Patients with Pneumonia-caused Death and Non-pneumonia-caused Death as the Underlying Cause of Death.

	Pneumonia-caused death (underlying) n = 76	Non-pneumonia-caused death (underlying) n = 128	p value
Male – no. (%)	32 (42.1)	51 (39.8)	0.770
Age of dementia onset- yr	78 (71 – 84)	77 (70 – 84)	0.595
Age of death - yr	85 (80 – 91)	85 (79 – 91)	0.622
Subtype of dementia – no. (%)			
AD	29 (38.2)	32 (25.0)	0.047
DLB	10 (13.2)	32 (25.0)	0.049
VaD	15 (19.7)	36 (28.9)	0.181
AGD	6 (7.9)	9 (7.0)	0.819
PSP	10 (13.2)	1 (0.8)	< 0.001
Others	6 (7.9)	18 (14.1)	0.186
Pneumonia complication			
Pneumonia as a reason for admission	15 (19.7)	25 (19.5)	1.000
Pneumonia during hospitalization	67 (88.2)	103 (81.1)	0.239
Comorbidities			
Hypertension	17 (22.4)	37 (28.9)	0.329
Diabetes Mellitus	13 (17.1)	14 (10.9)	0.285
Heart failure	2 (2.6)	14 (10.9)	0.056
Cerebral infarction	18 (23.7)	34 (26.6)	0.740
Malignant neoplasm	6 (7.9)	14 (10.9)	0.628
Fractures	28 (36.8)	46 (35.9)	1.000
Parkinson disease	4 (5.3)	9 (7.0)	0.771
Clinical conditions			
Dysphagia	48 (63.2)	63 (49.2)	0.053
PEG	26 (34.2)	47(36.7)	0.764
BMI at admission- median (IQR) (n = 85)	18.7 (16.4 - 21.1)	18.7 (17.2 - 20.8)	0.550
Weight of brain at death, g - median (IQR) (n = 113)	1,132 (1,036 – 1,200)	1,070 (986 - 1,185)	0.326
Medications			
Benzodiazepines use	8(10.5)	14 (10.9)	1.000
No. of medications (≥ 5)	17 (35.4)	19 (22.1)	0.095

AD: Alzheimer's diseases, DLB: Dementia with Lewy Bodies, VaD: Vascular dementia, AGD: Argyrophilic grain disease, PSP: Progressive supranuclear palsy, PEG: percutaneous endoscopic gastrostomy, BMI: body mass index, IQR: interquartile range

(underlying) group. In the grouping of immediate cause of death, 90 (44.1%) were assigned to the pneumonia-caused death (immediate) group and 114 (55.9%) to the non-pneumonia caused death (immediate) group. Comparisons between the groups in each death group are shown in Tables 1 and 2.

The comparisons between the pneumonia-caused death (underlying) group and the non-pneumonia-caused death (underlying) group are shown in Table 1. There were no significant differences between the two groups with regard to gender, or the age at the onset of dementia and death. There incidence of pneumonia complications during the hospitalizations did not differ to a statistically significant extent between the two groups, and more than 80% of the patients developed pneumonia during hospitalization in both the pneumonia-caused death (underlying) and the non-pneumonia-caused death (underlying) groups. Dysphagia tended to be more common in the pneumonia-caused death (underlying) group than in the non-pneumonia-caused death (underlying) group (Table 1).

The comparisons between the pneumonia-caused death (immediate) group and the non-pneumonia-caused death (immediate) group are shown in Table 2. Gender-male pre-

sented a significant difference between the groups. With regard to the subtypes of dementia, only in VaD was a significant difference between the groups with a higher number of non-pneumonia-caused death (Table 2). The incidence of pneumonia during hospitalization was significantly higher in the pneumonia-caused death (immediate) group. With regard to the incidence of comorbidities, although there were no differences in the underlying causes of death of the two groups (Table 1), there were more patients with malignant neoplasms than those in the non-pneumonia-caused death (immediate) group (Table 2). Other factors, including the performance of percutaneous endoscopic gastrostomy (PEG), the body mass index (BMI) at admission, and the brain weight were not significantly different between the pneumonia-caused death (underlying) and non-pneumonia-caused death (underlying) groups or between the pneumonia-caused death (immediate) and non-pneumonia-caused death (immediate) groups (Table 1, 2, respectively).

Pneumonia-caused issues among the subtypes of dementia

Pneumonia related issues including the incidence of pneumonia before and after hospital admission and pneumonia-

Table 2. Characteristics of Patients with Pneumonia-caused Death and Non-pneumonia-caused Death as the Immediate Cause of Death.

	Pneumonia-caused death (immediate) n = 90	Non-pneumonia-caused death (immediate) n = 114	p value
Male – no. (%)	44 (48.9)	39 (34.2)	0.044
Age of dementia onset- yr	77 (70 – 84)	77 (71 – 84)	0.792
Age of death - yr	85 (79 – 91)	85 (79 – 91)	0.777
Subtype of dementia – no. (%)			
AD	31 (34.4)	30 (26.3)	0.221
DLB	23 (25.6)	19 (16.7)	0.163
VaD	15 (16.7)	36 (31.6)	0.022
AD & VaD	1 (1.1)	3 (2.8)	0.632
AGD	7 (7.8)	8 (7.0)	1.000
PSP	8 (8.9)	3 (2.6)	0.063
Others	6 (6.7)	18 (15.8)	0.045
Pneumonia complication			
Pneumonia as a reason for admission	20 (22.2)	20 (17.5)	0.403
Pneumonia during hospitalization	89 (98.9)	81 (71.7)	< 0.001
Comorbidities			
Hypertension	20 (22.2)	34 (29.8)	0.254
Diabetes Mellitus	10 (11.1)	17 (14.9)	0.534
Heart failure	6 (6.7)	10 (8.8)	0.613
Cerebral infarction	20 (22.2)	32 (28.1)	0.419
Malignant neoplasm	3 (3.3)	17 (14.9)	0.008
Fractures	35 (38.9)	39 (34.2)	0.558
Parkinson disease	5 (5.6)	8 (7.0)	0.778
Clinical condition			
Dysphagia	52 (57.8)	59 (51.8)	0.400
PEG	32 (35.6)	41 (36.0)	1.000
BMI – median (IQR) (n = 99)	18 (16 – 21)	20 (18 – 21)	0.401
Weight of brain – median (IQR) (n = 176)	1,100 (985 – 1,193)	1,070 (1,005-1,170)	0.379
Medications			
Benzodiazepines use	11 (12.2)	11 (9.6)	0.651
No. of medications (≥ 5)	8 (10.5)	14 (10.9)	1.000
	15 (23.8)	21 (29.6)	0.559

AD: Alzheimer's diseases, DLB: Dementia with Lewy Bodies, VaD: Vascular dementia, AGD: Argyrophilic grain disease, PSP: Progressive supranuclear palsy, PEG: percutaneous endoscopic gastrostomy, BMI: body mass index, IQR: interquartile range

caused death were compared among the subtypes of dementia (Table 3). Although the frequency of pneumonia-caused death, both as an underlying and an immediate cause of death, was high in all subtypes of dementia, in both cases, the frequency was highest among the patients with progressive supranuclear palsy (PSP). The second highest frequency of pneumonia-caused death (underlying) was observed among the patients with AD and argyrophilic grain disease (AGD), while the second highest frequency of the pneumonia-caused death (immediate) was observed among patients with DLB and AD. When comparisons were made within the types of dementia, the rates of pneumonia-caused death (underlying) and pneumonia-caused death (immediate) among patients with AD were found to be similar (underlying, 47.5%; immediate, 50.8%; $p=0.856$); in contrast, there was a significant difference in the rates in DLB patients (underlying, 23.8%; immediate, 54.8%) ($p=0.007$). Pneumonia was an underlying and an immediate cause of death in equal numbers of VaD patients.

A high frequency of pneumonia complications was observed in all subtypes of dementia. Most notably, 10 of the 11 patients who were diagnosed with PSP developed pneumonia during hospitalization and died as a result of pneu-

monia; in each of these cases, pneumonia was the underlying cause of death. Dysphagia was observed in more than 50% of patients with AD, DLB and VaD and in 81.8% of patients with PSP.

Factors influencing pneumonia-related death in patients with dementia

The risk factors for pneumonia-caused death, (both underlying and immediate) were determined using logistic regression models. Dysphagia, diabetes mellitus, AD, AGD, and PSP were risk factors for pneumonia-caused death (underlying). Heart failure was inversely associated with the pneumonia-caused death (underlying) (Table 3). Male gender and the incidence of pneumonia during hospitalization were risk factors for pneumonia-related death (immediate). The presence of a malignant neoplasm was inversely associated with pneumonia-caused death (immediate) (Table 4).

Discussion

The present study on patients with neuropathologically-confirmed dementia revealed that pneumonia was common cause of death both as immediate and underlying causes of

Table 3. Pneumonia-related Issues according to Subtypes of Dementia.

	AD n = 61	DLB n = 42	VaD n = 51	AGD n = 15	PSP n = 11	Others n = 24	Total n=204
Age at dementia onset –median (IQR)	79 (73-84)	77 (71-84)	76 (69-83)	75 (69-82)	87 (74-95)	70 (57-76)	77 (70-84)
Age at death–median (IQR)	85 (80-90)	84 (81-91)	83 (77-87)	80 (72-97)	92 (88-97)	77 (65-80)	85 (79-91)
Gender, male-n (%)	20 (32.8)	12 (28.6)	27 (52.9)	6 (40.0)	7 (63.6)	11 (45.8)	83 (40.7)
Pneumonia complication							
Pneumonia as a reason for admission	12 (19.7)	9 (21.4)	8 (15.7)	4 (26.7)	3 (27.3)	4 (16.7)	40 (19.6)
Pneumonia during hospitalization	54 (88.5)	38 (90.5)	41 (80.4)	12 (85.7)	10 (90.9)	15 (62.5)	170 (83.7)
Cause of death							
Pneumonia-caused death (underlying)	29 (47.5)	10 (23.8)	15 (29.4)	6 (40.0)	10 (90.9)	6 (25.0)	76 (37.7)
Pneumonia-caused death (immediate)	31 (50.8)	23 (54.8)	15 (29.4)	7 (46.7)	8 (72.7)	6 (25.0)	90 (44.1)
Comorbidities							
Hypertension	18 (29.5)	8 (19.0)	18 (35.3)	1 (6.7)	2 (18.2)	7 (29.2)	54 (26.5)
Diabetes Mellitus	8 (13.1)	1 (2.4)	11 (21.6)	0 (0.0)	1 (9.1)	6 (25.0)	27 (13.2)
Heart failure	5 (8.2)	0 (0.0)	3 (5.9)	2 (13.3)	1 (9.1)	5 (20.8)	16 (7.8)
Clinical conditions							
Dysphagia	31 (50.8)	28 (66.7)	26 (51.0)	5 (33.3)	9 (81.8)	12 (50.0)	111 (54.4)
PEG	19 (31.1)	15 (35.7)	24 (47.1)	4 (26.7)	4 (36.4)	7 (29.2)	73 (35.8)
BMI at admission- median (IQR) (n = 85)	18 (16-20)	18 (14-21)	19 (18-21)	18 (14-19)	19 (18-22)	19 (18-24)	19 (17-21)

AD: Alzheimer's diseases, DLB: Dementia with Lewy Bodies, VaD: Vascular dementia, AGD: Argyrophilic grain disease, PSP: Progressive supranuclear palsy, PEG: percutaneous endoscopic gastrostomy, BMI: body mass index IQR: interquartile range

Table 4. Factors Relating to Pneumonia as the Underlying Cause of Death in Patients with Dementia Using Logistic Regression Model.

	Coefficient	SE	p value	OR	95% CI
Dysphagia	0.715	0.342	0.036	2.045	1.047-3.994
Diabetes mellitus	1.126	0.490	0.022	3.084	1.180-8.061
Heart failure	-1.902	0.894	0.033	0.149	0.026-0.861
Alzheimer's disease	1.062	0.349	0.002	2.891	1.459-5.730
Argyrophilic grain disease	1.147	0.618	0.064	3.148	0.937-10.577
Progressive supranuclear palsy	3.553	1.128	0.002	34.921	3.826-318.775

SE: standard error, OR: odds ratio, CI: confidence interval. p value: chi-square test

Baseline adjustment covariates: sex, onset age, subtypes of dementia, comorbidities, incidence of pneumonia, comorbidities (hypertension, diabetes mellitus, heart failure, cerebral infarction, malignant neoplasm, fracture), dysphagia, and percutaneous endoscopic gastrostomy.

death. The factors associated with pneumonia-caused death (underlying) included the subtype of dementia (AD, AGD, and PSP), dysphagia, and diabetes mellitus; while the factors associated with pneumonia-caused death (immediate) included male gender and the incidence of pneumonia during the hospitalization (irrespective of the subtype of dementia).

Hospital-acquired pneumonia (HAP) is relatively common during hospitalization and it is also associated with an increased mortality and an increased length of stay (15, 16). Several studies of patients with dementia have reported that a high proportion of deaths can be attributed to pneumonia (4-8). However, the frequency of pneumonia-caused death in patients with dementia seems to vary due to factors such as the source of information, study design, and the subtypes and severity of dementia (7). To clarify the potential reasons for these varying results, we evaluated patients with neuropathologically-confirmed dementia and examined the risk factors for pneumonia-caused death both as the underlying- and the immediate-cause of death. All of the patients were in the terminal stage of their illness and died in hospital. In the present study, the rates of pneumonia-caused death (underlying) and pneumonia-caused death (immediate)

were 37.7% and 44.1%, respectively. These frequencies of pneumonia-caused death were almost compatible with previous reports which examined patients with autopsy-confirmed dementia (4, 6, 10, 11).

Dysphagia was the only factor (along with dementia subtype) that increased the risk of pneumonia-caused death (underlying) (Table 4). Dysphagia, which is defined as difficulty in swallowing, may occur due to oropharyngeal or esophageal problems (17) and can be a major factor in the development of pneumonia (18-20). Patients with dementia usually develop dysphagia in the most advanced stage of their disease (21). Most of our patients were in the terminal stage of their illness and their cognitive impairments were often severe. As a result, with the exception of the patients with AGD, more than 50% of our patients presented dysphagia; the prevalence of dysphagia differed according to the type of dementia (Table 3). Although we could not examine the swallowing function of the patients in the terminal stage of dementia, the prevalence of dysphagia was highest among patients with PSP (81.8%) followed by DLB (66.7%), AD (50.8%), and VaD (51.0%). The impairment of saliva swallowing and the aspiration of swallowed material into the airway can cause aspiration pneumonia (22). A re-

Table 5. Factors Relating to Pneumonia as the Immediate Cause of Death in Patients with Dementia Using Logistic Regression Model.

	coefficient	SE	p value	OR	95% CI
Pneumonia complication during hospitalizations	3.484	1.032	0.001	32.579	4.308-246.370
Gender-Male	0.723	0.321	0.024	2.060	1.098-3.864
malignant neoplasm	-1.512	0.683	0.027	0.220	0.058-0.840

SE: standard err, OR: odds ratio, CI: confidence interval. p value: chi-square test

Baseline adjustment covariates: sex, onset age, subtypes of dementia, comorbidities, incidence of pneumonia, comorbidities (hypertension, diabetes mellitus, heart failure, cerebral infarction, malignant neoplasm, fracture), dysphagia, and percutaneous endoscopic gastrostomy.

cent study indicated the existence of a relationship between dysphagia and aspiration pneumonia (23). The different prevalence of dysphagia might be risk factor for death due to aspiration pneumonia depending on the subtype of dementia. These differences are also thought to be caused by lesions in diffuse areas of the brain, which result in cognitive disorders and the deterioration of the oral, pharyngeal, and laryngeal functions (24). A meta-analysis suggested that the prevalence of swallowing difficulties in the different types of dementia ranges from 13 to 57% and that the prevalence of swallowing difficulties in patients with DLB was higher than that in patients with AD (25). The present study also showed that the prevalence of dysphagia in patients DLB was higher than that in patients with AD (Table 3). The frequency of pneumonia-caused death (immediate) was also high among patients with DLB. The highest prevalence of dysphagia was observed in patients with PSP; in most of these patients, pneumonia was an underlying- or immediate-cause of death. These results indicate that dysphagia started a chain of events leading to the development of pneumonia and ultimately, to death.

In the present study, AD, AGD, and PSP (but not on DLB and VaD) were evaluated as risk factors for pneumonia-caused death (underlying) (Table 3). An autopsy study by Magaki et al. reported that the rate of pneumonia-caused death (both underlying and immediate) was high in patients with moderate and severe AD (8). In the present study, although a greater number of patients with DLB were classified into the non-pneumonia-caused death (underlying) group than the pneumonia-caused death (underlying) group ($p=0.049$, Table 1), there was no significant difference in the number of patients with DLB who were classified into the pneumonia-caused death (immediate) and non-pneumonia-caused death (immediate) groups ($p=0.163$, Table 2). Severe cardiac and circulatory autonomic dysfunction as well as respiratory dysfunction occurs in DLB (26-28), but not in AD. This suggests a clue as to why pneumonia might result in the further aggravation of cardiac and circulatory dysfunction in patients with DLB once they reach the terminal stage of their disease, when pneumonia can lead to death due to a decreasing ventilatory response to hypercapnia (28). The more patients with VaD in the non-pneumonia-caused death (immediate) group than those in the pneumonia-caused death (immediate) group was observed ($p=0.002$, Ta-

ble 2). VaD, which is associated with cerebral infarctions, was associated with a lower risk of pneumonia-caused death (immediate). Although previous studies have indicated an association between dysphagia and stroke (29), further studies are needed to confirm the relationship between pneumonia-caused death and cerebrovascular lesions. Despite the small number of patients with PSP and AGD, these factors were associated with a higher risk of pneumonia-caused death (underlying). This result, with regard to PSP, was compatible with previous studies that concluded that the incidence of dysphagia among patients with PSP is high from the early stage of the disease and which found that the rate of pneumonia-related death among patients with PSP was high (30). However, there is currently little information in relation to PSP and AGD and further studies are needed to confirm these results.

Diabetes mellitus was the only comorbidity that was found to be a risk factor for pneumonia-caused death (underlying) (Table 3). It has been reported that cognitive impairments, especially AD and other forms of dementia, are frequent comorbidities in patients with patients with diabetes mellitus. The insulin resistance caused by diabetes mellitus may lead to a lack of physical activities as well as immune dysfunction (31). Patients with diabetes mellitus develop infections more frequently than non-diabetic individuals (32). The result indicated that appropriate and careful clinical treatment is essential for diabetes mellitus, even if it is difficult owing to their cognitive impairments. Heart failure was inversely associated with pneumonia-caused death (underlying), while and malignant neoplasms were inversely associated with pneumonia-caused death (immediate) (Table 4, 5). This means that the condition of these patients was likely to have been poorer than that of the patients without these comorbidities. Such patients may be more likely to die due to heart failure or complicated conditions caused by malignancy before they develop HAP.

Pneumonia during hospitalization, and male gender were risk factors for pneumonia-caused death (immediate) (Table 4). This result may suggest that the risk of pneumonia is independent from the type of dementia and that it has stronger influence on patient death than other factors in the terminal stage of dementia. Pneumonia-caused death (immediate) may be influenced by functional deterioration due to aging together with dementia. With regard to respiratory

conditions in older adults, several major important physiological changes occur with aging, including a decrease in the elastic recoil of the lung, a decrease in the compliance of the chest wall, and a decrease in the strength of the respiratory muscles (3). These conditions may be more likely to lead to death once older adults develop pneumonia in the terminal stage of their life. The cognitive and functional deterioration that are caused by any form of dementia may contribute to the deterioration of respiratory conditions that occurs with aging. Consequently, the incidence of pneumonia during hospitalization was a risk factor for pneumonia-caused death (immediate) with a high odds ratio.

The present retrospective observational study has some limitations. Although the patients underwent brain autopsy at the study site, we were unable to compare the data with data from control patients without dementia due to the ethics surrounding autopsy examinations. The data related to dysphagia was mostly collected from the observations of the clinicians in charge, without specialized swallowing assessments. In addition, this study was conducted at a single medical institute. Further studies in older adults in different medical settings are therefore necessary before the results can be generalized.

In conclusion, our observational study of patients with autopsy-confirmed dementia revealed that different factors were associated with pneumonia-caused death depending on whether pneumonia was the underlying or the immediate cause of death. Certain subtypes of dementia (AD, AGD, and PSP) were associated with pneumonia-caused death (underlying), but not pneumonia-caused death (immediate). Dysphagia and comorbid diabetes mellitus as well as pneumonia complication during hospitalization were important factors that should be considered in directing the optimal clinical management of patients with dementia. Our results may be incorporated into clinical practices on management of patients with dementia in the terminal-stage. The study warrants further investigations, particularly in the form of a prospective cohort study.

The authors state that they have no Conflict of Interest (COI).

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