TSUKUBA UNIVERSITY
GRADUATE SCHOOL OF COMPLEHENSIVE HUMAN SCIENCES
筑波大学大学院人間総合科学研究科

Dissertation

博士論文

Prognosis of patients with dementia complicated with pneumonia

（肺炎合併に伴う認知症患者の予後についての検討）

by

TOSHIE MANABE
間　辺　利　江

2016

CONTENTS

CHAPTER 1. PREFACE

I. Backgrounds ・・・・・・・・・・・・・・・・・・・・・・・・・・・・・5

II. Objectives ・・・・・・・・・・・・・・・・・・・・・・・・・・・・・6

III. Frameworks ・・・・・・・・・・・・・・・・・・・・・・・・・・・・10

CHAPTER 2. LITERATURE REVIEWS AND CONCERNIG ISSUES・・・12

I. Dementia ・・・・・・・・・・・・・・・・・・・・・・・・・・・・・13

A. Alzheimer's diseases ・・・・・・・・・・・・・・・・・・・・・15

B. Dementia with Lewy bodies ・・・・・・・・・・・・・・・・・・16

C. Vascular dementia ・・・・・・・・・・・・・・・・・・・・・17

D. Other subtypes of dementia ・・・・・・・・・・・・・・・・・・18

II. Cause of death and pneumonia-associated mortality on patients with dementia and the difficulties for their evaluations ・・・・・・・・・・・・・・・・・20

III. Time from dementia onset to mortality (survival-time) on patients with dementia・・・・・・・・・・・・・・・・・・・・・・・・・・・・・21

IV. Pneumonia in older adults・・・・・・・・・・・・・・・・・・・・・22

CHAPTER 3. CAUSE OF DEATH ON PATIENTS WITH DEMENTIA (STUDY 1) ・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・25

I. Objectives ・・・・・・・・・・・・・・・・・・・・・・・・・・・・26

II. Methods ・・・・・・・・・・・・・・・・・・・・・・・・・・・・27

A. Study design and subjects ・・・・・・・・・・・・・・・・・・・・27

B. Diagnosis and definition ・・・・・・・・・・・・・・・・・・・・28

C. Statistical analysis ・・・・・・・・・・・・・・・・・・・・・29

D. Ethics ・・・・・・・・・・・・・・・・・・・・・・・・30

III. Results ・・・・・・・・・・・・・・・・・・・・30

A. General characteristics of patients Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and vascular dementia (VaD) ・・・・・・・・30

B. Cause of death in patients with dementia ・・・・・・・・31

IV. Discussions ・・・・・・・・・・・・・・・・・・・・・・・・32

V. Conclusions ・・・・・・・・・・・・・・・・・・・・・・・・34

CHAPTER 4. INFLUENCES OF PNEUMONIA COMPLICATION ON THE PROGNOSIS IN PATIENTS WITH AUTOPSY CONFIRMED ALZHEIMER'S DISEASE, DEMENTIA WITH LEWY BODIES AND VASCULAR DEMENTIA (STUDY 2) ・・・・・・・・・・・・・・・・・・・・・・・・35

I. Objective ・・・・・・・・・・・・・・・・・・・・36

II. Methods ・・・・・・・・・・・・・・・・・・・・38

A. Study design and subjects ・・・・・・・・・・・・・・・38

B. Diagnosis and definitions ・・・・・・・・・・・・・・・40

C. Statistical analysis ・・・・・・・・・・・・・・・・・・41

III. Results ・・・・・・・・・・・・・・・・・・・・42

A. General characteristics of study patients with AD, DLB, and VaD ・・42

B. Clinical time course of dementia in dementia patients with and without pneumonia ・・・・・・・・・・・・・・・・・・・・43

C. Risk factors relating to survival time in dementia patients using the Cox proportional hazard model ・・・・・・・・・・・・・・・・・・・45

IV. Discussion ・・・・・・・・・・・・・・・・・・・・・・45

V. Conclusion ・・・・・・・・・・・・・・・・・・・・・・50

CHAPTER 5. PROGNOSTIC FACTORS OF DEMENTIA WITH LEWY BODEIS COMPICATED WITH PNEUMONIA (STUDY 3) ・・・・・・・・52

I. Objective ・・・・・・・・・・・・・・・・・・・・・・53

II. Methods ・・・・・・・・・・・・・・・・・・・・・・54

A. Study design and subjects ・・・・・・・・・・・・・・・・・・54

B. Diagnosis and definitions ・・・・・・・・・・・・・・・・・・55

C. Statistical analysis ・・・・・・・・・・・・・・・・・・57

D. Ethics ・・・・・・・・・・・・・・・・・・57

III. Results ・・・・・・・・・・・・・・・・・・・・・・58

A. General characteristics of study patients with dementia with Lewy bodies (DLB) ・・・・・・・・・・・・・・・・・・・・・・58

B. Clinical conditions of patients with DLB at death ・・・・・・・・59

C. Evaluation of the factors associated with the time from DLB onset to death ・・・・・・・・・・・・・・・・・・・・・・59

IV. Discussion ・・・・・・・・・・・・・・・・・・・・・・60

V. Conclusion ・・・・・・・・・・・・・・・・・・・・・・64

CHAPTER 6. **DISCUSSIONS** ・・・・・・・・・・・・・・・・・・・・・・66

I. Discussions ・・・・・・・・・・・・・・・・・・・・・・67

II. Limitations and requirements for the further studies ・・・・・・73

CHAPTER 7. CONCLUSIONS 74

ACKNOWLEGEMENTS 77

REFERENCES 80

TABLES AND FIGURES 103

CHAPTER 1. PREFACE

CHAPTER 1. PREFACE

I. Backgrounds

The growing aged population is a critical social issue worldwide. In Japan, the ministry of Health, Labour and Welfare (MHLW)– Japan estimated that the people aged ≥ 65 yr. would leach approximately 40% of total population in 2055 [MHLW, 2014]. Aging is not only an immediate personal issue but also a salient factor in public health and medical care concerns. The enhancements of policy making for caring older adults and the clinical practice on any healthcare settings have been challenging.

Dementia is increasingly becoming a major healthcare challenge as the population ages [Ferri CP, et al., 2005]. In globally, the World Health Organization (WHO) currently estimated that the number of people living with dementia worldwide is 47.5 million and is predicted to increase to 75.6 million by 2030 [WHO, 2016]. In Japan, it has been estimated that the 4.6 million of individuals have been facing to dementia and its number would increase to over 7 million in 2025 which is the 20% of population aged ≥65 yrs. [MHLW, 2012].

Dementia is a condition in which there is progressive deterioration in cognition that affects daily function including memory, thinking, and the ability to perform

activities of daily living [Todd S, et al., 2013; Anderson K, et al., 1997]. It is an umbrella term that occurs when the brain is affected by certain diseases or conditions. Since a first case of Alzheimer's disease (AD) was reported in 1907 [Alzheimer A. (Translated by LJ and HG), 1987], currently, many different types of dementia were determined. Some are far more common than others. In Japan, AD is the most common subtype of dementia [Ikejima C, et al., 2012; Matsui Y, et al., 2009] and is called three major subtypes of dementia together with dementia with Lewy bodies (DLB), and Vascular dementia (VaD). Those three major subtypes of dementia encompass approximately 90% of the total population of dementia in Japan [Akatsu H, et al., 2002; Kosaka K, et al., 1999]. However, in terms of DLB, it has been only forty-years after the first report on the pathology of DLB by Kosaka et al [Kosaka K, et al., 1976]. The detailed pathophysiology of DLB has not yet been fully understood [McKeith IG, et al., 2000; Lopez OL, et al., 2002]. The additional studies on DLB are urgently required.

Clinical diagnosis of subtypes of dementia is important because of the differences in disease prognosis and management of mental and functional disorder. The confirmation of subtypes of dementia requires ultimately the neuropathological examination based on the autopsy. The inaccuracy of clinical diagnosis of dementia as well as discrepancies between death certificate and autopsy-confirmed diagnoses on

subtypes of dementia has been well documented [Attems J, et al., 2004; Fu C, et al., 2004; Kannoun S, et al, 2000; Kukull WA, et al., 1994; Osbye T, et al., 1999].

Persons with dementia tend to die at an earlier age compared persons without dementia [Todd S, et al., 2013; Maregoni A, et al., 2011]. The previous study indicated the varied time from dementia onset to death (survival-time) among subtypes of dementia [Stubendorff K, et al., 2011; MacKhann G, et al., 1984; Cercy SP, et al., 1997]. The comparison of survival-time between AD and DLB were controversial; faster [Olichney JM, et al., 1998], slower [Stavitsky K, et al., 2006] or no difference [Helmes E, et al., 2003; Ballard C, et al., 2001; Williams MM, et al., 2006; Lopez OL, et al., 2000].

Pneumonia is one of the major frightened infectious disease which associate to mortality and morbidity in older adults [Janssens JP, et al., 2004]. The previous studies indicated that dementia is one of the risk factors for occurring pneumonia [Manabe T, et al., 2015; Taylor JK, et al., 2013]. Several studies also reported an association between dementia and increased risk of death from pneumonia [Fu C, et al., 2004; Kannoun S, et al, 2000; Kukull WA, et al., 1994; Inagaki T, et al., 1992]. Pneumonia can be a primary cause of mortality in patients with dementia, while cardiovascular disease and neoplasms are common in the general population [Fu C, et al., 2004; Kukull WA, et al.,

1994; Attems J, et al., 2005]. A meta-analysis indicated that the odds of pneumonia-associated mortality were increased more than two fold in patients with dementia than those without dementia [Foley NC, et al., 2015]. However, the disease progression of dementia with and without pneumonia have not been previously elucidated. In addition, the factors relating to the survival-time on patients with dementia who complicated with pneumonia have remained unclear.

Although the examinations for effects of pneumonia both for mortality and morbidity in older adults with dementia is crucial, the results among previous studies concerning to survival-time, frequency of pneumonia complication and pneumonia-associated mortality on patients with dementia have varies and have not been fully elucidated. It can be hypothesized that these differences may result from the heterogeneity among the studies including the cause of death (underlying or immediate), the method used to obtain the cause of death (autopsy or death certificate), the subtypes and severity of dementia, and the study design (population-based cohort, observational in a hospital, or community-based).

II. Objectives

The aim of the present study was elucidating the effects of pneumonia for the

disease prognosis and prognostic factors on neuropathologically confirmed patients with different subtypes of dementia. In order to achieve thestudy objectives, three studies have been conducted. The purpose on each study were: (Study 1) to describe the cause of death; (Study 2) to evaluate and compare the survival-time (time from the dementia onset to death) among patients with AD, DLB, and VaD, and to assess prognostic factors on patients with AD, DLB, and VaD; (Study 3) to examine the survival-time and prognostic factors on patients with DLB.

Findings from this study would be the important implications for present and future clinical managements on patients with dementia for maximizing their life-expectancies.

III. Frameworks

Frameworks of the present study is as follows: (Fig. 1-1)

STUDY 1.

Study 1 observed the general and clinical characteristics of study patients including frequency of pneumonia complication and examined the cause of death on patients with Alzheimer's disease (AD), Dementia with Lewy bodies (DLB), and vascular dementia (VaD). The effect of pneumonia complication to their cause of death, especially to

pneumonia-associated mortality was compared among AD, DLB, and VaD.

STUDY 2.

Study 2 examined the survival-time on patients with AD, DLB, and VaD and compare its differentiations among subtypes of dementia.

Study 2 also assessed the prognostic factors to the survival-time on patients with AD, DLB, and VaD.

STUDY 3.

Study 3 examined the time from dementia onset to mortality (survival-time) and the prognostic factors on patients with DLB.

DISCUSSION

Following to the aim of the study, the disease prognosis of patients with dementia complicated pneumonia were comprehensively discussed based on outcomes on the above three studies and related issues.

CHAPTER 2. REVIEWS AND CONCERNING ISSUES

CHAPTER 2. LITERATUR REVIEWS AND CONCERNING ISSUES

In this chapter, trends and concerning issues for conducting clinical study on disease prognosis on dementia together with pneumonia would be summarized.

I. Dementia

Dementia is one of the major causes of disability and dependency among older people worldwide. In globally, the WHO reported that 47.5 million people have dementia and there are 7.7 million new cases every year [WHO, 2015]. In Europe, the prevalence of dementia ranged from 0.9% at age 65 – 69 years to 40.7% at 90 years and over with an incidence of 63.5 per 1,000 persons/year at 90 years of age and older [Ott A., et al. 1995]. In Japan, the prevalence of dementia according to 5-year age strata between 65 and 99 years was 5.8 – 77.7 % [Ikejima C, et al. 2012]. Thus, dementia is increasingly taking an important role on healthcare as the population ages in globally [Ferri CP, et al. 2005].

Dementia includes a group of related neurodegenerative disorders which caused by physical changes and accumulations of abnormal proteins in the brain. It is defined as chronic deterioration of intellectual function and cognitive skills significant enough to interface with the ability to perform daily activities. The main features of dementia are reduced cognitive ability, neurological and psychiatric symptoms, and functional disability [Fermandez M, et al., 2010]. Dementia also brings impacts on caregivers, families and societies.

Since a first case of Alzheimer's disease (AD) was reported in 1907 by Alzheimer [Alzheimer A. (Translated by LJ and HG), 1987], the researches on dementia has been expanding. Currently, there are many different forms of dementia were found, while some are far more common than others. Alzheimer's disease is the most common cause of dementia. The forms and affected areas of accumulating abnormal proteins cause the various subtypes of dementia. They also lead to clinical symptoms and disease progressions on patients with dementia. Therefore, a diagnosis of dementia can only be confirmed by neuropathological-autopsy.

A. Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder that causes an insidious decline in cognitive function. AD is the most frequent cause of dementia which covers approximately 50% of all dementia patients in Japan [Mhlw. 2014]. In the US, a study estimated that there were 4.7 million individuals aged 65 years or older with AD dementia and the total number of people with AD dementia in 2050 is projected to be 13.8 million, with 7.0 million aged 85 years or older [Herbert LE, et al., 2013]. A diagnosis of AD can be confirmed the detection of extracellular plaques containing Aβ peptides and intracellular neurofibrillary tangles (NFT) composed of the neuron-enriched, microtubule-associated protein (MAP), tau. The classic hallmarks are progressive deterioration of memory, language, and intellect. AD is associated with an increased mortality [Mölsä PK, et al., 1986]. Sleep and circadian rhythm disorders are clearly more frequent in AD than in the general population, and it has been reported that up to 45% of patients may have sleep problems [Pistacchi M, et al., 2014; Moran M, et al., 2005]. The greatest risk factor for AD is age and the chances of developing the disease increases two-fold every 5 years after age 65. As Sleep-related breathing disorders (SRBDs) are very frequent in AD patients and in this group are clearly more prevalent than in the general population [Ancoli-Ysrael S, et al., 1991].

B. Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies (DLB) is the second most common degenerative dementia disorder, after Alzheimer's disease (AD) together with vascular dementia (VaD). The first autopsied case of DLB was reported in 1976 by Kosaka et al [Kosaka K, et al., 1976] and proposed the term in 1980 [Kosaka K, et al. 1980]. Currently, it covers 10 – 20% of total population of dementia in Japan. DLB is characterized neuropathologically by the presence of Lewy bodies (LB), containing α–syncline, in the brainstem and the cerebral cortex of patients [Kosaka K, et al., 1984; Perry RH, et al., 1990]. The course of DLB starts with a primary lesion usually in the cerebral cortex and the brainstem, and may also spread to the peripheral autonomic nervous system [Horimoto Y, et al., 2003]. DLB presents the various neurological disorders including repetitive consciousness. The core clinical features of DLB are fluctuating cognitive dysfunction, visual hallucinations, and Parkinsonism. Autonomic dysfunctions are also commonly observed in patients with DLB [Yoshita M, et al., 2015]. Severe cardiac and circulatory autonomic dysfunction [Horimoto Y, et al., 2003; Allan LM, et al., 2007] occurs in DLB as well as respiratory dysfunction [Mizukami K, et al., 2009;]. Pneumonia is a common complication in patients with DLB patients [Lai EC, et al.,

2015; Yamamoto T, et al., 2010], and is the major cause of death [Hishikawa N, et al., 2003]. A decreased ventilator response to hypercapnia due to respiratory autonomic dysfunction [Mizukami K, et al., 2009] might contribute the disease progression of DLB complicated with respiratory infection.

It has been only 40 years since the first autopsy case of DLB was reported from Japan. The pathophysiology of DLB has not yet been fully elucidated and the diagnostic accuracy remains various [McKeith IG, et al., 2000; Lopez OL, et al., 2002].

C. Vascular dementia (VaD)

Vascular dementia (VaD) is the second largest cause of dementia in the older adults, representing 15-20% of all cases of dementia worldwide. VaD often contribute to cognitive impairments in AD and other forms of so-called “mixed dementias” [Langa KM, et al., 2004]. VaD is results from ischemic or hemorrhage cerebrovascular diseases, or hypoperfusive ischemic cerebral injury resulting from cardiovascular and circulatory disorders [Roman GC, et al., 1993]. The high prevalence of VaD in older adults is a reflection of the fact that stroke and ischemic heart disease are the two leading cause of morbidity and mortality in older adults [Roman GC, et al., 2002]. There are no pathological criteria for the diagnosis of VaD, unlike AD or DLB. Cognitive changes in

VaD are much more variable than in other forms of dementia, and are dependent on the particular neural substrates affected by the vascular pathology. Symptoms of VaD include memory loss and difficulties with thinking, problem-solving or language. There is a substantial overlap in neuropsychiatric features between AD and VaD, with a very high burden of all symptoms in both subtypes. Although average rate of cognitive decline are similar in VaD and AD, VaD has largely mortality because of cardiovascular and cerebrovascular causes. The reported mean survival was 3-5 years [Kua EH, et al., 2014].

D. Other subtypes of dementia and neurodegenerative diseases

Other than AD, DLB and VaD, currently, there are various subtypes of dementia are founded including Fronto-temporal dementia (FTD), progressive supranuclear palsy (PSP), Argyrophilic grain disease (AGD), along with the expansions of the scientific researches and elucidation on mechanism of dementia and neurodegenerative diseases.

PSP is a disorder of tau protein aggregation and is first described as a distinct disorder from Parkinson's disease in 1964 [Nagami A., et al., 2015]. At least half of the patients with PSP exhibit the classic bradykinesia with disproportionate postural

instability, erect posture with nuchal rigidity, frontal behavioral and cognitive changes, vertical gaze palsy, and other disabling brainstem deficits. Nonmendelian genetic risk factors exist, but PSP is almost entirely sporadic, with a prevalence of five to six persons per 100,000, mean onset age of 63, and median survival of 7 years [Golve LI. 2014].

AGD is a common neurodegenerative disease of older adults characterized by the presence of argyrophilic grains (Ags) together with pre-tangle neurons contain hyperphosphorylated 4R tauopathy. AGD was first described by Braak H and Braak E in 1987 and was characterized by Ags in the entorhinal Cortes, hippocampus, amygdala and neighboring temporal cortex in patients who had suffered from adults onset dementia [Braak H, et al., 1987]. In patients with AGD, behavioral abnormality changes and emotional and mood imbalance have been noted [Braak H, et al., 1998]. Togo et al also showed that amnesia, irritability and agitation, followed by delusions, dysphoria and apathy in older AGD patients who admitted to geriatric wards of mental hospitals [Togo T, et al., 2005]. There is no specific test for a clinical diagnosis of AGD. AGD and AD may occur in the same individual. Currently, the cause of AGD is still not known and AGD is still a poorly understood neurological disorder.

FTD is a neurodegenerative disorder characterized by behavioral abnormalities,

language impairment, and deficits in executive functions [Seelaar H., et al., 2010]. FTD is also characterized by early stages, usually named mild cognitive impairment (MCI), that are still not completely characterized. The diagnosis of FTD can be difficult because of its insidious and gradual onset, Misdiagnosis is common, and FTD is often mistaken for as Alzheimer's disease (AD) [Rankin KP, et al., 2004; Walker AJ, et al., 2005].

II. Cause of death and pneumonia-associated mortality on patients with dementia and the difficulties for their evaluations

Dementia covers a wide range of symptoms and encompasses a group of related neurodegenerative disorders. Therefore, many factors including comorbidities relating to mortality are likely to co-exist. Although cardiovascular diseases and neoplasms are more frequent causes of mortality in the general population, patients with dementia tend to die more often from infections, including pneumonia. In fact, the previous studies cited pneumonia as the most common cause of mortality in patients with dementia [Kukull WA, et al., 1994; Todd S, et al., 2013; Kammoun S, et al., 2000; Chamandy N, et al., 2005; Brunnström HR, et al., 2009; Fu C., et al., 2004]. However, in the previous studies, the frequency of pneumonia-associated mortality in subjects with dementia

varies and ranges from 12% to 70% [Magaki S, et al., 2014; Attems J, et al., 2005; Kukull WA, et al., 1994; Todd S, et al., 2013; Kammoun S, et al., 2000; Chamandy N, et al., 2005; Brunnström HR, et al., 2009; Fu C., et al., 2004]. These different frequencies of pneumonia-associated mortality among studies were shown in Table 2-1. These differences may be caused by the heterogeneity among these studies including the cause of death (underlying or immediate), the method used to obtain the cause of death (autopsy or death certificate), the subtypes and severity of dementia, and the study design (population-based cohort, observational in a hospital, or community-based).

III. Time from dementia onset to mortality (survival time) on patients with dementia

The reported times on the time from dementia onset to mortality (survival time) of dementia was varied and different among the subtypes of dementia. In patients with AD, a study resulted the mean survival time after diagnosis of AD were 8-12 years [McKhann G, et al., 1984]. The other retrospective study in AD resulted the median survival from initial diagnosis was 4.2 years for men and 5.7 years for women [Larson EB, et al., 2004]. In patients with DLB, a meta-analysis resulted that mean illness durations in DLB were 1.8-9.5 years [Cercy SP, et al., 1997]. Previous reports indicated

the varied survival time on each subtype of dementia patients [Stubendorff K, et al., 2011; MaKhann G, et al., 1984]. The comparison of survival time between AD and DLB were controversial; faster [Olichney JM, et al., 1998], slower [Stavitsky K, et al., 2006] or no difference [Helmes E, et al., 2003; Ballard C, et al., 2001; Williams MM, et al., 2006; Lopez OL, 2000].

One of the reasons of these differences survival times of AD and DLB might cause the heterogeneity among studies that mentioned in previous section. The most previous studies involved the lack of autopsy confirmation for the subtype of dementia. The survival time on patients with dementia complicated with pneumonia has rarely evaluated previously.

IV. Pneumonia in older adults

Pneumonia is a leading cause of hospitalisation and mortality among older adults, particularly those aged ≥85 years [Kaplan V, et al., 2002; Loeb M, et al., 1999]. Aging associated with a progressive decrease in lung performance. In addition, the various comorbidities on alder adults affects to their respiratory systems. In a previous study indicated that the mortality rate for older patients with community-acquired pneumonia (CAP) was high as 30% and nursing-home acquired pneumonia (NHAP) may reach 57% [El-Solh AA, et al., 2000]. The diagnosis of pneumonia in this age

group is often delayed because of the frequent absence of fever, the absence of cough, and changes in mental status. Hospitalization for CAP is also an indicator of adverse prognosis in older patients. A population based case-control study resulted that 1-year mortality in CAP vs. the control population in hospital were 41 % vs. 29%, respectively [Kaplan V, et al., 2003].

There were various factors relating to develop pneumonia in older adults were previously reported. Dementia is the one of the factors [Manabe T, et al., 2015]. Pneumonia is also a major cause of death in older adults with dementia [Magaki S, et al., 2014; Attems J, et al., 2005; Kukull WA, et al., 1994; Todd S, et al., 2013; Kammoun S, et al., 2000; Chamandy N, et al., 2005; Brunnström HR, et al., 2009; Fu C., et al., 2004] . A meta-analysis indicated that the odds of pneumonia-associated mortality were increased more than two fold in subjects with dementia than those without dementia [Foly NC, et al., 2015]. There are many therapeutic guidelines for CAP and healthcare-associated pneumonia (HCAP) [ATS/ISDA. 2005; JRS. 2006; JRS. 2009]. The American Thoracic Society and Infectious Diseases Society of America have proposed guidelines on HCAP that cover CAP and HCAP, including for patients in nursing homes [ATS/ISDA. 2005]. HCAP in the United States is mostly characterised by infection with multidrug-resistant pathogens. HCAP and nursing and

healthcare-associated pneumonia (NHCAP) in Japan are rarely related to multidrug-resistant pathogens, and have a worse clinical outcome than those in CAP due to comorbidity related to dysphagia or aspiration [Polverino E, et al., 2013; Fukuyama H, et al., 2013]. Several studies have indicated that 7–24% of CAP is due to aspiration [Marrie TJ, et al., 1990; Leroy O, et al., 1997]. A report in Japan indicated that over 60% of hospitalised patients with CAP can be diagnosed with aspiration pneumonia [Teramoto S, et al., 2008]. Aspiration pneumonia increases with age and if patients live in nursing homes [Muder RR, et al., 1998].

Along with the rapid growth of high aging society, the places for providing medical care for old adults would be expanding as well as place to live. Unless diseases and cognitive disorders affected, the respiratory system remains capable of maintaining adequate gas exchange during the entire life span. The attention for managing pneumonia on older adults with dementia needs to be straightened.

CHAPTER 3.

Cause of death and its comparison among patients with Alzheimer's disease, dementia with Lewy bodies, and vascular dementia (Study 1)

CHAPTER 3. Cause of death on patients with dementia

In this chapter, the effect of pneumonia complication to disease mortality was discussed based on the examination for the cause of death on patients with dementia and the differentiations of causes of death among Alzheimer's diseases (AD), Dementia with Lewy Bodies (DLB), and Vascular dementia (VaD).

I. Objectives

Dementia is a major predictor of death together with other age-associated conditions [Baldereschi M, et al., 1999]. Several study indicated that dementia contributes the shortness of life spam [Todd S, et al., 2013]. However, patients' cognitive decline does not always reflect the duration or time course of dementia. Pneumonia is common infection and lead to mortality in older adults with dementia [Magaki S, et al., 2014; Attems J, et al., 2005; Kukull WA, et al., 1994; Todd S, et al., 2013; Kammoun S, et al., 2000; Fu C., et al., 2004]. A meta-analysis indicated that the odds of pneumonia-associated mortality were increased more than two fold in subjects with dementia than those without dementia [Foly NC, et al., 2015]. However, in the previous studies, the frequency of pneumonia-associated mortality in patients with dementia

varies and ranges from 12% to 70%. These differences may result from 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), the subtypes and severity of dementia, and the study design (population-based cohort, observational in a hospital, or community-based).

The aim of the present study was to evaluate the cause of death, both as the underlying and immediate cause for evaluating how pneumonia-associated mortality affected in patients with autopsy-confirmed dementia. It also compared the cause of death among the different subtypes of dementia: AD, DLB, and VaD.

II. Methods

A. Study design and subjects

The present study was a retrospective observational study. The study site was Choju Medical Institute, Fukushimura Hospital in Toyohashi, Japan, which mainly specializes in psychogeriatrics, neurology, internal medicine, and surgery including the Neuropathological research center [Akatsu H, et al., 2002]. The study subjects were hospitalized and deceased patients between January 2005 and December 2014. All patients had brain autopsies in the Neuropathological research center at the study site. The data relating to the general and clinical backgrounds of the patients, clinical time

courses, clinical conditions on patients during the hospitalization including swallowing dysfunction, nosocomial infections, percutaneous endoscopic gastrostomy (PEG), medications, and results of neuropathological examinations were collected from the patients' charts, medical reports, and autopsy reports with the results of neuropathological examinations was collected. From the all autopsied cases during the observational period, the patients with neuropathological diagnosis of AD, DLB, or VaD by the specialized pathologists and neurologists were selected for the present study. The cases co-existed both with AD and vascular pathology (i. e. mixed dementia) were considered to have AD.

B. Diagnosis and definitions

Two investigators independently reviewed the data with masked clinical diagnoses written by the physician in charge to ensure the accurate subtype of dementia and cause of death. The cause of death, subtype of dementia, and other variables were extracted into predesigned data collection forms. We verified the accuracy of the data by comparing the collection forms from each investigator. Any discrepancy was resolved by discussion.

The complication of pneumonia was repetitive pneumonia during the

hospitalization once and over based on the diagnosis criteria of guidelines for the management of hospital-acquired pneumonia in adults by the Japanese Respiratory Society [JRS 2009].

The immediate cause of death was defined as the final disease, injury, or complication directly causing death. The underlying cause of death was defined as the disease, injury, or corresponding circumstances that initiated the chain of events ultimately leading to death [Brunnström HR, et al., 2009].

C. Statistical analysis

The data relating to the general and clinical backgrounds of the patients, clinical time courses including time to death from dementia onset, time to hospital admission from dementia onset and time to death from hospital admission, and causes of death were summarized and compared among groups of each subtype of dementia. The Kruskal–Wallis tests were used for continuous variables, and the Chi-squared and Fisher's exact tests were used for categorical variables. Data analyses were conducted using SPSS Statistics 22.0 (IBM, Armonk, NY, USA). For all analyses, significance levels were two tailed, and $p<0.05$ was considered significant.

D. Ethics

The study was approved by the Institutional Review Boards of the University of Tsukuba and Choju Medical Institute, Fukushimura Hospital. Written informed consent was obtained from patients' relatives.

III. Results

A. General characteristics of patients Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and vascular dementia (VaD)

During the observation period, a total of 261 patients died and were autopsied at Fukushimura Hospital (Fig. 3-1). After excluding the patients who died within 1 week of an emergency visit to the hospital and who did not have data available, a total 230 patients were included in the study. Among them, the total 157 patients who determined AD, DLB and VaD by neuropathological diagnoses were eligible in the present study patients. The numbers of each subtype of dementia were 63 AD (40.1%), 42 DLB (26.8%), and 52 VaD (33.1%).

The general characteristics of the patients with AD, DLB, and VaD are shown in Table 3-1. While more female patients were seen in AD and DLB, more male patients were observed in VaD than female. The age of dementia onset in VaD tended younger than those in AD and DLB, but no significant difference among the subtype of dementia.

The high incidence of pneumonia complication was seen in all three subtypes of dementia with no significant difference among the three groups. DLB presented the highest incidence (90.5%) of pneumonia complication. Cerebral infarction including asymptomatic condition was pathologically found 82.7% of patients in VaD and it was also seen in AD and DLB with the high incidence. The major comorbidities were hypertension and diabetes mellitus, especially in patients with VaD.

B. Causes of death in patients with dementia

The underlying and immediate causes of death were examined and compared among the subtypes of dementia (Table 3-2).

Although the causes of death in dementia patients were varied, pneumonia was the greatest underlying and immediate cause of death, which presented 49.2% of AD patients in the underlying cause of death (p=0.001) and over 50% of AD and DLB patients in the immediate cause of death (p=0.007) with the significant difference among the subtypes of dementia. More patients had respiratory failure as the immediate cause of death in VaD and DLB than in AD (p=0.056). Renal failure was the second highest immediate cause of death in VaD with a significant difference among the subtypes (p=0.046). Sudden death only presented in DLB as an immediate cause of

death.

IV. Discussions

Although differentiation between the clinical diagnosis of dementia and the judgment of post-mortem diagnosis has been discussed [Snowden JS, et al., 2011], the most previous studies involved the lack of autopsy confirmation for the subtype of dementia. In the present study, the subtypes of dementia was neuropathlogically diagnosed and compared among AD, DLB and VaD. The present study revealed that patients with all three major subtype of dementia complicated with pneumonia with high incidence. Especially, over 90% of patients with DLB had pneumonia complication during the hospitalization. This was the compatible results with the several investigations that indicated a high proportion of pneumonia in subjects with dementia has been reported [Magaki S, et al., 2014; Attems J, et al., 2005; Kukull WA, et al., 1994; Todd S, et al., 2013; Kammoun S, et al., 2000; Brunnström HR, et al., 2009; Fu C., et al., 2004]. Along with the high proportion of pneumonia, approximately 50% of patients in AD, DLB, and VaD presented the swallowing dysfunctions. This is thought to be caused by lesions in diffuse areas of the brain, resulting in disorders in cognition and changes in oral, pharyngeal, and laryngeal functions [Suh MK, et al., 2009]. A study

indicated that subjects with dementia usually develop swallowing dysfunctions during the course of the illness, commonly in the advanced stage of dementia [Feinberg MJ, et al., 1992]. Most of the patients were at the terminal stage and their cognitive impairments might be often severe. Swallowing dysfunctions may start as a chain of events leading to developing pneumonia. A study indicated [Wada H, et al., 2001] that the mid-stage of AD may result in aspiration pneumonia due to silent dysphagia. It can be speculated that the majority of the pneumonia complication was due to aspiration pneumonia.

In the comparison among AD, DLB and VaD, cerebral infarction and hypertention were more common comorbidity in VaD than in AD and DLB. VaD is a progressive disease that is caused by reduced cerebral blood flow supplying the brain, and may associate with some types of cerebral events [Venkat P, et al., 2015]. The proportions of other comorbidities were similar among three major subtypes of dementia.

Pneumonia and heart failure were the main cause of death on dementia patients both in immediate and underlying cause of death which was the compatible results with the previous autopsy studies [Attems J, et al., 2005; Brunnström HR, et al., 2009]. As the comparison between underlying and immediate cause of death on each subtype of

dementia, although the main cause of death in patients with DLB was heart failure as the underlying cause of death, but was pneumonia in the immediate cause of death (Table 3-2). Severe cardiac and circulatory autonomic dysfunction [Yoshita M, et al., 2015; Allan LM, et al., 2007; Mizukami K, et al., 2009] as well as respiratory dysfunction [Mizukami K, et al., 2009] occurs in DLB, but not in AD. It has been thought that pneumonia results in further aggravation of cardiac and circulatory dysfunction in patients with DLB while once they reach the terminal stage, pneumonia can lead to mortality, due to decreasing ventilator response to hypercapnia [Mizukami K, et al., 2009].

In the present study, it was unable to evaluate the cause of death in patients without dementia. This was a limitation of this study and further study requires the comparison between patients with and without dementia.

V. Conclusion

In conclusion, pneumonia incidence was high in three different autopsy confirmed subtypes of dementia. Pneumonia and heart failure were the main cause of death both in immediate and underlying cause of death. These results warrant the further study including the comparison with non-dementia patients.

CHAPTER 4.

Influences of pneumonia complication on the prognosis in patients with autopsy confirmed Alzheimer's disease, dementia with Lewy bodies, and vascular dementia (Study 2)

CHAPTER 4. Influences of pneumonia complication on the prognosis in patients with autopsy confirmed Alzheimer's disease, dementia with Lewy bodies, and vascular dementia

In this chapter, influences of pneumonia complication on the survival-time in patients with autopsy confirmed Alzheimer's disease, dementia with Lewy bodies, and vascular dementia have been discussed.

I. Objectives

Dementia is becoming an illness of major concern in the aging population globally. Although there is an individual variability in the clinical course, dementia decreases people's life expectancy [Alzheimer's Association, 2013; Lobo A, et al., 2000; Meguro K, et al., 2002]. The primary cause of death in dementia patients is pneumonia, while cardiovascular disease and neoplasms are more common in the general population [Magaki S, et al., 2014; Brunnström HR, et al., 2009; Fu C., et al., 2004]. A recent meta-analysis indicated that the odds of pneumonia-associated death were increased in persons with dementia [Foly NC, et al., 2015]. Although there were few reports investigating the association between respiratory function and dementia [Vidal JS, et al.,

2013; Pathan SS, et al., 2011; Guo X, et al., 2007], a current UK study demonstrated an association between forced expiratory volume in 1 second (FEV_1) and dementia-related death [Russ TC, et al., 2015]. It can hypothesize that if deterioration in pulmonary function contributes to death in dementia, dementia patients who develop pneumonia would have shorter life spans than those without pneumonia. Understanding the influence of pneumonia on clinical time course of dementia is crucial forpredicting the remaining life in patients with dementia and would contribute to develop the optimal clinical management of dementia.

Currently, there are three major subtypes of dementia: Alzheimer's disease (AD); dementia with Lewy bodies (DLB); and vascular dementia (VaD). These encompass approximately 90% of the total dementia population in Japan [Akatsu H, et al., 2002]. However, the previous study indicated the varied survival-time on each subtype of dementia [Stubendorff K, et al., 2011; MacKhann G, et al., 1984; Cercy SP, et al., 1997]. The comparison of survival time between AD and DLB were controversial; faster [Olichney JM, et al., 1998], slower [Stavitsky K, et al., 2006] or no difference [Helmes E, et al., 2003; Ballard C, et al., 2001; Williams MM, et al., 2006; Lopez OL, et al., 2000].

The disease progression of AD, DLB, and VaD with and without pneumonia has not previously been elucidated and remained unclear. However, some discrepancies between the clinical and neuropathological diagnoses of each subtype of dementia sometimes make it difficult to interpret the results of such studies [Magaki S, et al., 2014].

The aims of the present study were to examine the survival time in AD, DLB, and VaD, with and without pneumonia and to determine the risk factors on the time from dementia onset to death.

II. Methods

A. Study design and subjects

The retrospective study was conducted at the Choju Medical Institute, Fukushimura Hospital in Toyohashi, Japan, which mainly specializes in psychogeriatrics, neurology, internal medicine, and surgery including the Neuropathological research center. The data were collected from patients' charts, medical reports, and autopsy reports with the results of neuropathological examinations, on hospitalized and deceased patients between January 2005 and December 2014. All patients had brain autopsies in the Neuropathological research center at the study site.

Data relating to the general and clinical backgrounds of the patients, clinical time courses, clinical conditions on patients during the hospitalization including swallowing dysfunction, nosocomial infections, percutaneous endoscopic gastrostomy (PEG), medications, and results of neuropathological examinations was collected.

From the all autopsied cases, the patients with neuropathological diagnosis of AD, DLB, or VaD by the specialized pathologists and neurologists were selected for the study. According to the criteria [McKeith IG, et al., 2005; McKeith IG, 2006; Kosaka K. 1990], low likelihood cases with extensive AD pathology was excluded. In addition, AD and vascular pathology are co-existed, Although if both AD and vascular pathology are remarkable, cases with those pathology are often called as mixed dementia, in the present study such cases were included in AD.

The clinical and general backgrounds, the incidence of pneumonia, underlying and immediate causes of death, and clinical time courses were compared among these three groups of subtype of dementia. The risk factors for the time to death from dementia onset (survival time) were analyzed for all eligible patients, and between patients with and without pneumonia.

The study was approved by the Institutional Review Boards of the University of Tsukuba and Choju Medical Institute, Fukushimura Hospital. Written informed

consent was obtained from patients' relatives.

B. Diagnosis and definitions

Two investigators independently reviewed the data with masked clinical diagnoses written by the physician in charge to ensure the accurate subtype of dementia and cause of death. The cause of death, subtype of dementia, and other variables were extracted into predesigned data collection forms. We verified the accuracy of the data by comparing the collection forms from each investigator. Any discrepancy was resolved by discussion.

The neuropathological diagnosis of each subtype of dementia, AD, DLB and VaD, was assessed using autopsy records.

The complication of pneumonia was repetitive pneumonia during the hospitalization once and over based on the diagnosis criteria of guidelines for the management of hospital-acquired pneumonia in adults by the Japanese Respiratory Society [JRS, 2009].

Dementia onset was defined at the time (year) when patients first experienced forgetfulness, disorientation, abnormal behavior, or delusions according to the Guideline

for Dementia 2010 [JSN, 2010]. Hospital admission was defined as the time of hospitalization that patients discharged.

The immediate cause of death was defined as the final disease, injury, or complication directly causing death. The underlying cause of death was defined as the disease, injury, or corresponding circumstances that initiated the chain of events ultimately leading to death [Brunnström HR, et al., 2009].

C. Statistical analysis

The data relating to the general and clinical backgrounds of the patients, clinical time courses including time to death from dementia onset, time to hospital admission from dementia onset and time to death from hospital admission, and causes of death were summarized and compared among groups of each subtype of dementia. The Kruskal–Wallis tests were used for continuous variables, and the Chi-squared and Fisher's exact tests were used for categorical variables. As the stratified analysis, the survival-time on patients with- and without-pneumonia on each subtype of dementia were compared using box plot. Survival curves of the number of years on survival times of dementia in groups of AD, DLB, and VaD with or without pneumonia were analyzed by the Kaplan–Meier method and comparisons were made using the log-rank test. To

evaluate independent factors for the survival time of dementia, a step-wise method was used for a Cox proportional hazard analysis. Data analyses were conducted using SPSS Statistics 22.0 (IBM, Armonk, NY, USA). For all analyses, significance levels were two tailed, and $p<0.05$ was considered significant.

III. Results

A. General characteristics of study patients with AD, DLB, and VaD

During the observation period, a total of 261 patients died and were autopsied at Fukushimura Hospital (Fig. 2-1). After excluding the patients who died within 1 week of an emergency visit to the hospital and who did not have data available, a total 230 patients were included in the study. Among them, the total 157 patients who determined AD, DLB and VaD by neuropathological diagnoses were eligible in the present study patients. The numbers of each subtype of dementia were 63 AD (40.1%), 42 DLB (26.8%), and 52 VaD (33.1%).

The general characteristics of the patients with AD, DLB, and VaD are shown in Table 2-1. While more female patients were seen in AD and DLB, more male patients were observed in VaD than female. The age of dementia onset in VaD tended younger than those in AD and DLB, but no significant difference among the subtype of dementia.

The high incidence of pneumonia complication was seen in all three subtypes of dementia with no significant difference among the three groups. DLB presented the highest incidence (90.5%) of pneumonia complication. Cerebral infarction including asymptomatic condition was pathologically found 82.7% of patients in VaD and it was also seen in AD and DLB with the high incidence. The major comorbidities were hypertension and diabetes mellitus, especially in patients with VaD.

B. Clinical time course of dementia in dementia patients with and without pneumonia

The clinical time courses on dementia patients were compared among the subtypes of dementia and between patients with and without pneumonia (Table 4-1). Although there was no difference on the age of dementia onset in three groups, the age of death were younger in VaD compared with those of AD and DLB (p=0.018). The median survival time in VaD was shorter (5 years) than those of AD (8 years) and DLB (8 years). Although the number of patients with DLB who did not acquire pneumonia was small, survival-time was shortened by 5 years if DLB patients developed pneumonia (13 vs 8 years) (p=0.048, Fig. 4-1). In the analysis on the divided survival time course, a significant differences was seen between the subtypes of dementia in the

time from dementia onset to hospital admission, but no difference was observed in the time from hospital admission to death.

The influence of the complication of pneumonia on clinical time courses were assessed by the Kaplan–Meier method and compared between the different subtypes of dementia using the log-rank test (Fig. 4-2). In the evaluation of the dementia patients (n = 157) and in the dementia patients with pneumonia (n=137) revealed significant differences among the subtypes of dementia (p<0.001 and p=0.002, respectively) (Fig. 4-2, A and B), However, there were no significant differences among the subtypes of dementia in the patients without pneumonia (Fig. 4-2, C).

As the sub-group analysis, the influence of the complication of pneumonia on clinical time courses were also assessed among different age groups by the Kaplan–Meier method using the log-rank test (Fig. 4-3). It was observed that the group of patients aged ≥75yr. was shorter survival time of dementia if pneumonia complicated than those aged <65yr. and 65 – 74 yr. Although the number of patients without pneumonia was small, there was no significant difference among aged groups on dementia duration.

Evaluation of risk factors time to death from dementia onset

C. Risk factors relating to survival time in dementia patients using the Cox proportional hazard model

Factors relating to the survival time of dementia were evaluated using the Cox proportional hazard model for dementia patients with and without pneumonia (n=157). The results indicated that the risk factors associated with the shorter survival time were gender-male, pneumonia, comorbidity of diabetes mellitus, age at dementia onset- ≥75 yr. and VaD. Age at dementia onset- < 65 yr. was associated to the longer survival time of dementia. The interaction of pneumonia vs. subtypes of dementia was examined by this model, and no statistical significance was observed.

D. Discussion

The present study, using neuropathological diagnoses of dementia, revealed that patients with all three major subtype of dementia complicated with pneumonia with high incidence. The medians of total survival time of dementia onset were 8 years in AD and DLB, and 5 years in VaD. The patients with VaD had shorter period of survival time than those of AD and DLB. The factors associating with shorter time of survival time of dementia were gender-male, pneumonia complication, diabetes mellitus, age at dementia onset- ≥75 yr., and VaD.

The World Health Organization has reported that 47.5 million people have dementia and there are 7.7 million new cases every year [WHO 2015]. In the current situation, the medications for treating dementia are limited. The development of optimal clinical management strategies for dementia is an urgent requirement for achieving the long life. Pneumonia is the leading cause of death in an aging population and, in the present study, pneumonia was the main cause of death on dementia patients which was the compatible results with the previous autopsy studies [Attems J, et al., 2005; Brunnström HR, et al., 2009]. The evaluation of effect of pneumonia in the life span for dementia patients is also crucial. However, the reported times on the survival time of dementia was varied. The effect of pneumonia on the survival time of dementia and its differences in subtypes of dementia were also unclear. Previous reports resulted that mean durations in DLB were 1.8-9.5 years [Cercy SP, et al., 1997]. A study resulted the mean survival time after diagnosis of AD were 8-12 years [Stavitsky K, 2006]. The other retrospective study in AD resulted the median survival from initial diagnosis was 4.2 years for men and 5.7 years for women [Larson EB, et al., 2004]. In the present study, the median survival time were 8 years in AD and DLB, and 5 years in VaD. One of the reasons of these differences survival times of AD and DLB might cause the accuracy of clinical diagnosis of dementia. Although differentiation between the clinical diagnosis of

dementia and the judgment of post-mortem diagnosis has been discussed [Snowden JS, et al., 2011], the most previous studies involved the lack of autopsy confirmation for the subtype of dementia. In the present study, the subtypes of dementia was neuropathlogically diagnosed and evaluated the survival time of dementia. The results in the present study of AD and DLB were similar to the mean duration of the 7.1 years in AD cases with post-mortem study [Armstrong RA. 2014] and slightly higher than 6.1 years evaluated by a meta-analysis in DLB [Cercy SP, et al., 1997]. The another reason was that the defined timing of initiation of dementia. Our evaluation was taken the disease duration from the time of disease onset, not from the time of diagnosis. In the results of previous study, the disease duration in AD and DLB examined from disease onset to death was similar, while those examined from time of diagnosis to death was significantly different [Stubendorff K, et al., 2011]. This may present the time difference of first awareness of condition and symptoms of dementia by the from an informant who knows the patient well. Additionally, we compared the survival time of AD and DLB with VaD. Although the etiopathogenesis of AD, DLB, and VaD are not completely understood, the differences in survival times might be due to the different pathogenesis of each type of dementia. VaD is a progressive disease that is caused by reduced cerebral blood flow supplying the brain, and may associate with some types of

cerebral events [Doody R, et al., 2005; Feldman HH, et al., 2009; Venkat P., et al., 2015]. In the present study, cerebral infarction was a more common comorbidity in VaD than in AD and DLB (p<0.001). Both AD and DLB are neurodegeneratative disease, and they may have slower progression than expansion of cerebral dysfunction of VaD. In addition, VaD has systemic vascular changes, and it is reasonable to suppose that these changes also, in part, contributing to shortening the survival time. In the present study, cerebral vascular changes were more common in patients with AD than those of DLB; however, no different of survival time between AD and DLB but with VaD.

Despite the subtype of dementia, many of the dementia patients experienced the complication of pneumonia. One of the reasons was that dementia patients may have weakened defense mechanisms for preventing respiratory tract infections. The previous studies revealed an association between respiratory function and cognition, which is impaired in dementia [Vidal JS, et al., 2013; Pathan SS, et al., 2011; Guo X, et al., 2007]. The deterioration of respiratory function may also influence to reduce the life time span once dementia patients experienced pneumonia. A recent study examining the association between respiratory function and the incidence of pneumonia indicated that for every 1 SD increase in FEV_1, the risk for the incidence of dementia decreased by more than 20% [Russ TC, et al., 2015]. The present study evaluated an association of

pneumonia not only for the death but also for the survival times in patients with dementia. Swallowing dysfunctions are common in patients with dementia, and known as the major contributor to the mortality [Rösler A, et al., 2015]. In this study, among AD, DLB, and VaD, the presentation of swallowing dysfunctions on each subtype of dementia were not significant difference (Table 4-1). It also did not evaluate as the influencing factor to the survival time. The results might indicate that the swallowing dysfunctions were the risk to mortality and survival time on patients with dementia, but regardless subtypes of dementia. Although the number of DLB patients without pneumonia was small, the survival time of patients with DLB and pneumonia was 5 years shorter than the survival time of patients with DLB but no pneumonia. On the other hand, similar survival times of dementia between with and without pneumonia were observed in AD and VaD (Table 3). This result suggested that if patients with DLB get pneumonia, the deterioration of the respiratory function may be faster than those of in other subtypes of dementia. One of the causes was that DLB decreased ventilator response to hypercapnia [Mizukami K, et al., 2009]. However, further investigations are needed to clarify this hypothesis.

The Cox proportional hazard model in the present study revealed that gender-male, pneumonia complication, comorbidity of diabetes mellitus, age at

dementia onset of ≥75yr., and VaD wereindependent risk factors relating to the shortness of survival time of dementia. Age at dementia onset of ＜65yr. influenced to the longer survival time of dementia (Table 4). Previously, type 2 diabetes mellitus has been known to hold a higher risk of dementia compared with the general population.[46,47] The present study evaluated that diabetes mellitus is also a risk for survival time for dementia patients. The results of present study suggested the importance of clinical management for repetitive pneumonia and underlying diseases including diabetes mellitus during the hospitalization on dementia patients, especially patients aged ≥75yr. for expanding patients' life span.

A limitation of this study was that the time of onset was taken from the medical records relying on reports from patients, patients' families, or care givers about the commencement of the symptoms and signs of dementia. The present study was conducted at an institute specialized in psychogerontology, particularly for patients with dementia. The physicians were specialists, with significant clinical experience in consulting with dementia patients. It was thought that the time discrepancy with the actual onset thought to be no wide range with their report. This study was conducted at a single medical institute, so further studies are required in other populations before the results can be generalized. However, as our understanding, these results are the first

report on comparisons of the survival time in dementia patients of AD, DLB, and VaD with and without pneumonia from Japan.

V. Conclusion

Pneumonia incidence was high in three different subtypes of dementia, and the risk of immediate cause of death in the patients. Pneumonia complication was a significant factor for disease prognosis in the dementia patient. To maximize life expectancy, the prevention of pneumonia and the appropriate clinical management of underlying diseases are necessary on dementia patients aged ≥75yr. These results warrant the further prospective cohort study.

CHAPTER 5.

Prognostic Factors Related to Dementia with Lewy Bodies Complicated with Pneumonia: An Autopsy Study (Study 3)

CHAPTER 5. Prognostic Factors Related to Dementia with Lewy Bodies Complicated with Pneumonia: An Autopsy Study

In this chapter, Risk factors for time to mortality on patients with autopsy confirmed Dementia with Lewy Bodies complicated with pneumonia have been discussed.

I. Objectives

Dementia with Lewy bodies (DLB) is the second most common degenerative dementia disorder, after Alzheimer's disease (AD). DLB is characterized neuropathologically by the presence of Lewy bodies (LB), containing α–synuclein, in the brainstem and the cerebral cortex of patients [Kosaka K, et al., 1984]. The core clinical features of DLB are fluctuating cognitive dysfunction, visual hallucinations, and parkinsonism. Pneumonia is a common complication [Yamamoto t, et al., 2010; Lai EC, et al., 2015;] and is the major cause of death in DLB patients (Hishikawa N, et al., 2003; Horimoto Y, et al., 2003) Susceptibility to pneumonia in DLB patients may, in part, be caused by aspiration due to swallowing dysfunction [Londos E, et al., 2013]. In addition, a previous report indicated that DLB patients have a decreased ventilator response to

hypercapnia due to respiratory autonomic dysfunction [Mizukami K, et al., 2009]. A decreased ventilator response results in the patient being more vulnerable to ventilatory failure during high-demand conditions, such as heart failure and pneumonia, possibly leading to poorer outcomes [Dyer C. et al., 2012]. It is plausible that decreased ventilator responses are also related to poor outcomes in DLB complicated by pneumonia. A study suggested that pneumonia is the most common cause of death in patients with DLB [Manabe T, et al., 2015]. Although it is well documented that pneumonia has a significantly negative impact on the prognosis in DLB, the factors affecting life expectancy in DLB patients with pneumonia have not yet been fully evaluated. The identification of such factors is thus important to achieve an improvement in both DLB patients' life expectancies and end-of-life care.

The purpose of the present study was to investigate the disease progression of neuropathologically-diagnosed DLB patients with pneumonia and to evaluate the risk factors influencing the survival time from the onset of DLB to death.

II. Methods

A. Study design and subjects

The present study was a retrospective observational study. The data in this

study were obtained from an observational study in which we studied autopsy cases of confirmed AD, vascular dementia (VaD), and DLB [Manabe T, et al., 2015]. The subjects included in the present study consisted of patients who were hospitalized, deceased, and underwent post-mortem autopsy at the Choju Medical Institute, Fukushimura Hospital, Toyohashi, Japan, between January 2005 and December 2014. Of the eligible patients, we selected 42 patients who had been neuropathologically diagnosed with DLB, and who had developed pneumonia during hospitalization. We retrospectively reviewed the patients' charts, medical reports, and autopsy reports along with the neuropathological examination results. Data on the general and clinical backgrounds of the patients, the incidence of pneumonia, comorbidities, autonomic dysfunctions, causes of death, and neuropathological examinations results were collected. The factors associated with survival time, defined as the time from the onset of DLB to death, were analyzed in all eligible DLB patients.

B. Diagnosis and definitions

The details of the neuropathological diagnosis of DLB and cause of death have been described in our previous study [Manabe T, et al., 2015]. For ensuring the

accuracy of the cause of death, including sudden death, two investigators independently reviewed the data with masked clinical diagnoses written by the physician in charge.

The occurrence of pneumonia was defined as pneumonia during hospitalization, once or more times, based on the diagnostic criteria established by the guidelines for the management of hospital-acquired pneumonia in adults by the Japanese Respiratory Society [JRS, 2009].

The time of dementia onset was defined as year when patients first experienced forgetfulness, disorientation, abnormal behavior, delusions, or visual hallucinations, according to the Guidelines for Dementia 2010 [JSN, 2010]. The duration of hospitalization was defined as the time from hospital admission until the patient's death.

Sleep disorders were diagnosed by physicians in charge if patients had sleeplessness complaints, reversed sleep-wake cycles, demonstrated confusion or other nursing problems at night time during hospitalization. Urinary incontinence, constipation, increased sputum production, and swallowing dysfunction were all clinically diagnosed by physicians specializing in geriatric medicine during the hospitalization.

C. Statistical analysis

General and clinical patient background data, the clinical time course (including survival time), and cause of death were summarized. As the median onset age of the patients was 78, they were divided into two groups according to their age (≤78 or ≥79 years of age) to analyze the effects in younger and older patients with DLB. For the patients with DLB complicated by pneumonia, survival curves of the time from DLB onset to death were analyzed by the Kaplan–Meier method, and comparisons were made using the log-rank test. To evaluate independent factors for the time from DLB onset to death, the step-wise method was used for the Cox proportional hazard model. Data analyses were conducted using the SPSS Statistics 22.0 software program (IBM, Armonk, NY, USA). For all analyses, significance levels were two tailed, and $p<0.05$ was considered to be significant.

D. Ethics.

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

III. Results

A. General characteristics of study patients with DLB

During the observation period, a total of 261 patients died and were autopsied at the study site. Of these, a total of 42 patients (30 females, 68.2%) were neuropathologically-diagnosed with DLB, and 39 (92.9%) of whom acquired pneumonia during hospitalization. The demographic and clinical characteristics of the DLB patients are shown in Table 5-1.

The median age of DLB onset was 78 years of age. Although the body mass index was unable to be measured in all patients owing to their physical conditions, this was low in most of the DLB patients at hospital admission. Cerebral infarction was pathologically observed in 35.7% of the DLB patients. Over 60% of the DLB patients had swallowing dysfunction. Sleeping disorders were observed in 52.4% of the patients, as were other common autonomic dysfunctions including constipation (81.0%), repeated falls (35.7%), and urinary incontinence (90.5%). The underlying conditions of hypertension, respiratory emphysema, and fractures of the femur were observed in more than 20% of the DLB patients.

B. Clinical conditions of DLB patients at death

Of the 39 DLB patients with pneumonia, the median age at death was 86 years (IQR, 81-91) with female patients on average older than male patients (Table 2). The median time from DLB onset to death was 8 years (IQR, 5-14). Male patients had a shorter period from the time of DLB onset to death than females.

Although the causes of death in the DLB patients varied, pneumonia was the most common (53.8%), followed by renal failure (15.4%) and respiratory failure (12.8%). Sudden death was observed in 10.3% of the DLB patients.

C. Evaluation of the factors associated with the time from DLB onset to death

The Kaplan–Meier curve in Fig. 1 shows the influence of age of onset, cerebral infarction, muscle weakness of the lower extremities, age at DLB onset, sleep disorder, and comorbidities including hypertension and respiratory emphysema, from the time of DLB onset to death. There were significant differences between the patients with and without cerebral infarction ($p=0.007$), with and without muscle weakness of the lower extremities ($P = 0.037$), and according to age ≤ 78 years or ≥ 79 years ($p < 0.001$). No significant differences were observed between the patients with and without sleep

disorder, or between those with and without the comorbidities investigated in this study.

In the DLB patients with pneumonia, the Cox proportional hazard model revealed a male sex (HR, 2.83), age of onset ≥78 years (HR, 4.71), cerebral infarction (HR, 2.36), and muscle weakness of the lower extremities (HR, 2.04) to be factors associated with the time from DLB onset to death (Table 3).

IV. Discussions

Of the patients with DLB in this study, only three did not develop pneumonia during hospitalization (Table 5-1), and pneumonia was the most common cause of death (Table 5-2) in those who were affected. Our results are consistent with those of previous studies, such as those reporting a high incidence of pneumonia [Yamamoto T, 2010; Lai EC, et al., 2015] and a high frequency of pneumonia-associated mortality in patients with DLB [Hishikawa N, et al., 2003]. The median time to death from DLB onset was 8 years (Table 2), while the reported survival-times of DLB were various and ranged from 1.8 to 9.5 [Cercy SP, et al., 1997]. One of the independent factors associated with disease progression in this study was cerebral infarction (Table 5-3).

We confirmed cerebral infarction by autopsy, and included asymptomatic and old cerebral infarctions. Although only a few studies have so far reported an association

between the clinical features and cerebrovascular lesions in DLB, a previous report indicated no greater susceptibility to death from stroke [Jellinger KA. 2003]. Although our data did not include any neuroimaging findings, our results indicated the possibility of the long-term influence of cerebral infarction, including asymptomatic cerebral infarction and a history of small cerebral infarctions, on the progression of DLB.

Muscle weakness of the lower extremities was observed in 33.3% of DLB patients (Table 5-1). Muscle weakness was also evaluated as a potential prognostic factor of DLB by the Cox proportional hazard model (Table 5-3). Although muscle weakness of the lower extremities is regarded as a risk factor for falls and fractures, in the present study, neither of these were associated with a shortened life expectancy in our study participants. It is important to bear in mind that previous studies indicated an association between muscle strength of the extremities and the risk of death in older adults, as well as a risk of lung function deterioration [Al Snih S, et al., 2002; Laukkanen P, et al., 2015]. In addition, a low pulmonary function was found to be associated with a low muscle mass in community-dwelling elderly people [Jeon YK, et al., 2015]. Similar to these observations, the results of the present study suggest that weakness of the extremities in DLB patients may be associated with a low respiratory function and thus aggravate the poor prognosis for patients with pneumonia. Along with

decreasing physical activity, the daily activities of a patient would decrease gradually and this might shorten the patients' life.

Although the smoking history of our patients was difficult to collect, quite a high incidence of respiratory emphysema was observed (Table 5-1). Liao et al. reported that in COPD patients with dementia, the incidence rate of hospital mortality was higher than those of dementia patients without COPD [Liao KM, et al., 2015]. In the present study, the Kaplan–Meier method failed to indicate any significant difference between patients with and without respiratory emphysema of the time from DLB onset to death (Fig. 5-1). This difference may be due to the fact that the deterioration of lung function in very older patients with DLB progresses regardless of a history of COPD.

Although the data on dysphagia was mostly collected from the observations of the clinicians in charge due to the difficulty to conduct conventional swallowing assessments [Teramoto S., et al., 2999] on this kind of group of patients, swallowing dysfunction was observed in 61.9% of the DLB patients (Table 5-1). It has been reported that susceptibility to pneumonia in DLB may be attributed to swallowing dysfunction [Shinagawa S, et al., 2009]. Despite the possibility that swallowing dysfunction may induce pneumonia, in the present study, this was not associated with a shortened life expectancy in DLB patients with pneumonia, and it also was not

identified as a prognostic factor in DLB with pneumonia (Table 5-3). Although the use of a percutaneous endoscopic gastrostomy tube (PEG) has been considered for the management of dysphagia, a meta-analysis concluded that PEG placement provided no evidence for an improvement in the long-term survival rates in patients with advanced dementia [Goldberg LS, et al., 2014]. The results of the present study are therefore compatible with the previous studies (Table 5-4).

We observed the available data for other factors related to autonomic dysfunction, including sleeping disorders, urinary incontinence, and constipation. However, these symptoms were not identified as useful prognostic factors in DLB (Table 5-3). A previous study in Sweden observing the 36-month survival of patients with DLB concluded that autonomic dysfunction, including orthostatic hypotension, incontinence, and constipation, were related to the survival time in patients with DLB [Stubendorff K, et al., 2012]. This discrepancy may also be due to the fact that the majority of patients presented with a high incidence of urinary incontinence and constipation during the course of the illness among the patients with DLB which and these frequencies were compatible with the findings of a previous report in Japan [Horimoto Y, et al., 2003].

The time of DLB onset was retrospectively estimated from the patients' medical records relying on reports from patients, patients' families, and/or caregivers about the commencement of the symptoms and initial signs of DLB. Thus, there may be a discrepancy between this and the actual time of onset. As the subjects of present study were pathologically confirmed DLB patients at a single center, the number of patients was thus quite small. Further studies are therefore required in alternative and larger populations before the results can be generalized and any definitive conclusions can be made. The diagnosis of pneumonia in this age group is often delayed because of the frequent absence of fever, the paucity or absence of cough, and changes in mental status (delirium) [Fein AM. 1994]. Therefore, it was no possible to examine the precise time from the occurrence of pneumonia to mortality. Due to the nature of this retrospective study, additional factors that may be related to disease progression in patients with DLB, such as orthostatic hypotension [Andersson M, et al., 2008], parkinsonism, nutrition support, and the reasons for hospital admission might exist, but they were not included in the analysis in the present study.

V. Conclusion

We found that the prognostic factors identified in autopsy-confirmed DLB

patients with pneumonia were pathologically-confirmed cerebral infarction, muscle weakness of the lower extremities, a male sex, and older age at onset (≥ 78 years). The careful management and the prevention of cerebral infarction and muscle weakness in DLB patients with respiratory tract infection are crucial factors for maximizing the patients' life expectancy, as well as for improving the patients' end-of-life care. The results of the present study warrant further prospective cohort studies with a larger group of patients.

CHAPTER 6.

DISCUSSIONS

CHAPTER 6. Discussions

In this chapter, outcomes studies 1 to 3 were discussed comprehensively for leading to the final conclusions on the present research.

I. Discussions

The present study intended to elucidate the disease prognosis and prognostic factors on neuropathologically confirmed patients with three major subtypes (AD, DLB, and VaD) of dementia complicated with pneumonia. The study revealed that the medians of total survival-time of dementia onset were 8 years in AD and DLB, and 5 years in VaD who complicated with pneumonia. The factors associating with shorter time of survival-time of dementia were pneumonia complication, gender-male, diabetes mellitus, older age at onset (≥75 yr.), and VaD. Among the patients with DLB complicated with pneumonia, the prognostic factors were cerebral infarction, muscle weakness of the lower extremities, gender-male, and older age at onset (≥ 78 years).

In recent years, dementia has been receiving increasing attention from governments, politicians, and medical providers in globally. However, dementia has only recently focused attention. Especially, the first case of pathology on DLB was

reported in 1976 [Kosaka K, 1976] and confirmed its terminology in 1980 [Kosaka K, 1980]. The additional scientific evidences, including the disease prognosis and the detailed pathophysiology are urgently required for developing effective clinical approaches, and maximizing the patients' life expectancy and the quality of remained life.

Dementia affects the life expectancy, living conditions, health profiles, and the characters on patients. Dementia also changes daily lives for families and care givers. The survival-time on patients with dementia and its risk factors are crucial information not only for clinical practices by medical providers but also for families and care givers and themselves.

Although it is generally accepted that pneumonia-associated mortality are more common in patients with dementia than those without dementia, the reported frequency of pneumonia-associated mortality in patients with dementia varies and ranges from 12% to 70% [Foly NC 2015]. The survival-time on patients with dementia that previously reported were also various, 8 - 12 years in AD [McKhann 1984] and 1.8 - 9.5 years in DLB [Cercy SP, 1997]. It can be thought that these differences caused by the heterogeneity among these studies including the cause of death (underlying or immediate), the methods of diagnosis (neuropathological or clinical) and the subtypes

and severity of dementia. In the present study, the subtypes of dementia were neuropathologically diagnosed by the expert pathologist in the study site and both immediate- and underlying-cause of death were examined. The most of patients were in the advanced stage of their illness. The survival-time of patients with AD and DLB complicated with pneumonia in the present study was 8 years which was the similar with the mean duration of the 7.1 years in AD with the previous autopsy study [Armstrong RA 2014] and slightly higher than 6.1 years evaluated by a meta-analysis in DLB [Cercy SP 1997] (Study 2). The survival-time of DLB patients without pneumonia complication was 5 years longer than those with pneumonia. Although the number of DLB patients without pneumonia was small, the more effects of pneumonia was possibly existed in DLB than those in AD.

The survival-time is shorter in patients with VaD than those in patients with AD or DLB. This difference may cause the different pathogenesis of each types of dementia. VaD is a progressive disease that is caused by reduced blood flow supplying the brain, and may associated with some types of cerebral events [Doody R 2005; Feldman HH 2009; Venkat P 2015]. In addition, VaD has systemic vascular damages, and it is reasonable to suppose that these damages, in part, contributing shortening the survival-time. In fact, cerebral infarction was a more common comorbidity in VaD than

in AD and DLB. AD and DLB are neurodegenerative diseases, and they may have slower progression than those of VaD with cerebral dysfunction. Therefore, this is the reasonable result. In addition, cerebral infarction was one of prognostic factor in the study only with DLB (Study 3). The result may suggest that cerebral infarction effects shortness of survival-time not only in dementia but also in DLB. The confirmation of this results on other forms of dementia requires the additional study with large population.

In patients with AD, DLB, and VaD, the risk factors associating with shorter survival-time of dementia were pneumonia complication, gender-male, diabetes mellitus, older age at onset (≥75 yr.), and VaD (Study 2). The high incidence of pneumonia complication was seen in all three subtypes of dementia with no significant difference among the three groups. DLB presented the highest incidence (90.5%) of pneumonia complication (Study 1) and the survival-time between with- and without pneumonia was significant (Study 2). Therefore, the prognostic factors of only in patients with DLB complicated with pneumonia were examined. The results indicated that the prognostic factors in patients with DLB complicated with pneumonia were pathologically-confirmed cerebral infarction, muscle weakness of the lower extremities, a male sex, and older age at onset (≥ 78 years) (Study 3). Previously, it has been known that type 2 diabetes mellitus hold a higher

risk of dementia compared with the general population. The result of the present study indicated that diabetes mellitus also hold as the prognostic risk to survival-time of the patients with dementia. Currently the continuous medication on aged patients have been on discussion. The result may suggest that the importance of continuous pharmacological management of diabetes mellitus, even patients were in the terminal stage of dementia. Gender-male presented a higher Hazard Ratio (HR) to the survival-time on patients with DLB comparing those on patients AD, DLB, and VaD. In the study on only with patients with DLB, muscle weakness of the lower extremities tended to effect to shorter survival-time on patients with DLB (Study 3). It is important to bear in mind that previous studies indicated an association between muscle strength of the extremities and the risk of death in older adults, as well as a risk of lung function deterioration [Al Snih S, et al., 2002; Laukkanen P, et al., 2015]. Similar to these observations, the results of the present study suggest that weakness of the extremities in DLB patients may be associated with a low respiratory function and thus aggravate the poor prognosis for patients with pneumonia. Along with decreasing physical activity, the daily activities of a patient would decrease gradually and this might shorten the patients' life. Although there were few reports investigating the association between respiratory function and dementia [Vidal JS, et al., 2013; Pathan SS, et al., 2011; Guo X, et al., 2007], a study in UK demonstrated an association between

forced expiratory volume in 1 second (FEV_1) and dementia-related death [Russ TC, et al., 2015]. These may suggested that the deterioration of lung function would risk to be dementia and the risk to shortness of life expectancy once dementia is occurred.

We intended to evaluate the effect of autonomic dysfunction using sleeping disorders, urinary incontinence, and constipation. However, these symptoms were not identified as prognostic factors in DLB. A previous study in Sweden observing the 36-month survival of patients with DLB concluded that autonomic dysfunction, including orthostatic hypotension, incontinence, and constipation, were related to the survival time in patients with DLB [Kaufnabb H 2004]. This discrepancy may also be due to the fact that the majority of patients presented with a high incidence of urinary incontinence and constipation during the course of the illness among the patients with DLB of which these frequencies were compatible with the findings of a previous report in Japan.

Swallowing dysfunction was observed over 40% of patients with AD and VaD and over 50% of patients with DLB (Study 2). Although the data on swallowing dysfunction was mostly collected from the observations of the clinicians in charge due to the difficulty to conduct conventional swallowing assessments on this kind of group of patients, it has been reported that susceptibility to pneumonia may be attributed to

swallowing dysfunction. It also approximately 20% of patients were hospitalized due to pneumonia (mostly clinically diagnosed aspiration pneumonia) (Supplemental study). Then, patients with dementia who admitted hospital due to pneumonia were hospitalized in shorter days than those due to other reasons (Supplemental study). However, the confirmation of effect of swallowing dysfunction to develop pneumonia including aspiration pneumonia and the survival time on patients with dementia requires the further investigation using the conventional swallowing assessments.

II. Limitations

The present study has several limitations. The time of dementia onset was retrospectively estimated from the patients' medical records relying on reports from patients, patients' families, and/or caregivers about the commencement of the symptoms and initial signs of dementia. There may be a difference between this and the actual time of onset. Patients of present study were conducted at a single center. Although the study site was the medical center that specialized for psychogeriatric and geriatric medicine, the survival-time on patients may influenced by the local therapeutic consensus and guidelines. The diagnosis of pneumonia in this age group is often delayed because of the frequent absence of fever, the paucity or absence of cough, and changes in mental

status (delirium). Therefore, it was not possible to examine the precise time from the occurrence of pneumonia to mortality. Due to the nature of this retrospective study, additional factors that may be related to disease progression in patients with dementia. However, they were not included in the analysis in the present study.

CHAPTER 7.

CONCOLUSIONS

CHAPTER 7. Conclusions

In this chapter, the significance results of studies 1, 2, and 3 were summarized as conclusions on the present study.

I. STUDY 1

The present study revealed that patients with all three major subtype of dementia complicated with pneumonia with high incidence. Especially, over 90% of patients with DLB had pneumonia complication during the hospitalization.

In the comparison among AD, DLB and VaD, cerebral infarction and hypertention were more common comorbidity in VaD than in AD and DLB.

As the comparison between underlying and immediate cause of death on each subtype of dementia, although the main cause of death in patients with DLB was heart failure as the underlying cause of death, but was pneumonia in the immediate cause of death.

II. STUDY 2

Patients with all three major subtype of dementia complicated with pneumonia with high incidence. The medians of total survival time of dementia onset were 8

years in AD and DLB, and 5 years in VaD. The patients with VaD had shorter period of survival time than those of AD and DLB. The factors associating with shorter time of survival time of dementia were gender-male, pneumonia complication, diabetes mellitus, age at dementia onset- ≥75 yr., and VaD.

III. STUDY 3

The prognostic factors identified in autopsy-confirmed DLB patients with pneumonia were pathologically-confirmed cerebral infarction, muscle weakness of the lower extremities, a male sex, and older age at onset (≥ 78 years).

The careful management and the prevention of diabetes mellitus in all three subtypes of dementia and cerebral infarction and muscle weakness in DLB with respiratory tract infection are crucial factors for maximizing the patients' life expectancy, as well as for improving the patients' end-of-life care. The results of the present study warrant further prospective cohort studies with a larger group of patients.

ACKNOWLEGEMENTS

ACKNOWLEGEMENTS

First of all, I would like to express my sincere appreciation to Dr. Katsuyoshi Mizukami, my supervisor, professor of Department of Social Health and Stress Management, University of Tsukuba Graduate School of Comprehensive Human Science. Dr. Mizukami gave me the unique idea of focusing on patients with dementia complicated with pneumonia. It became my research key word. Although the medical knowledge on dementia and neurodegenerative disorders were complicated for me, the extensive advices and suggestions from Dr. Mizukami brought me for conducting the successful clinical studies on dementia. I also express my sincere appreciation to Dr. Hiroyasu Akastu in Fukushimura Hospital and Nagoya City University School of Medicine. He cooperated me to examine the precious data that has been holding in Institute of Neuropathogoly, Fukushimura hospital. Without his outstanding support, I was not able to conduct the present study.

I also thank to Dr. Nobuyuki Hizawa and Dr. Shinji Teramoto in Department of Pulmonary medicine, Tsukuba University. Their opinions as the expert of pulmonary medicine and respiratory infections were very much appreciated. They also have been supporting as the supervisors for my double major Ph.D. program in Medicine.

I would thank to Mr. Seiji Nakamura and all of staffs and graduate students in the laboratory of Dr. for their kindly supports and encouragements.

Finally, I would like to express my deepest appreciation to Dr. Koichiro Kudo, former director of Disease Control and Prevention Center, National Center for Global Health and Medicine. His variable advices and suggestions as the expert of respiratory medicine and infectious diseases, warm supports, strong encouragements, and the long-term relationships as my mentor sparked my interest in clinical and epidemiological researches and the opportunity to earn Ph.D. degree.

Thank you very much.

REFERENCES

REFERENCES

Akatsu H, Takahashi M, Matsukawa N, Ishikawa Y, Kondo N, Sato T, Nakazawa H, Yamada T, Okada H, Yamamoto T, Kosaka K. Subtype analysis of neuropathologically diagnosed patients in a Japanese geriatric hospital. J Neurol Sci. 2002;196:63-9.

Al Snih S, Markides KS, Ray L, Ostir GV, Goodwin JS. Handgrip strength and mortality in older Mexican Americans. J Am Geriatr Soc. 2002;50:1250-6.

Allan LM, Ballard CG, Allen J, Murray A, Davidson AW, McKeith IG, Kenny RA. Autonomic dysfunction in dementia. J Neurol Neurosurg Psychiatry 2007;78: 671-677.

Alzheimer Alois. About a Peculiar Disease of the Cerebral Cortex. By Alos Alzheimer, 1907 (Translated by L. Jarvik and H. Greenson) Alzheimers Dis Assoc Disord 1987;1:3-8.

Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement. 2013;9:208-45.

American Thoracic Society and the Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and

healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

Ancoli-Israel S, Klauber MR, Butters N, Parker L, Kripke DF. Dementia in institutionalized elderly: relation to sleep apnea. J Am Geriatr Soc. 1991;39:258–263.

Andersen K, Lolk A, Nielsen H, Andersen J, Olsen C, Kragh-Sørensen P. Prevalence of very mild to severe dementia in Denmark. Acta Neurol Scand. 1997;96:82-7.

Andersson M, Hansson O, Minthon L, Ballard CG, Londos E. The period of hypotension following orthostatic challenge is prolonged in dementia with Lewy bodies. Int J Geriatr Psychiatry 2008;23:192-8.

Armstrong RA. Factors determining disease duration in Alzheimer's disease: a postmortem study of 103 cases using the Kaplan-Meier estimator and Cox regression. Biomed Res Int. 2014;623487.

Attems J, Arbes S, Böhm G, Böhmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. Wien Med Wochenschr. 2004;154:159-62.

Attems J, König C, Huber M, Lintner F, Jellinger KA. Cause of death in demented and non-demented elderly inpatients; an autopsy study of 308 cases. J Alzheimers Dis. 2005;8:57-62.

Baldereschi M, Di Carlo A, Maggi S, Grigoletto F, Scarlato G, Amaducci L, Inzitari D. Dementia is a major predictor of death among the Italian elderly. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology. 1999;52:709-13.

Ballard C, O'Brien J, Morris CM, Barber R, Swann A, Neill D, McKeith I. The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. Int J Geriatr Psychiatry. 2001;16:499-503.

Braak H, Braak E. Argyrophilic grains disease: frequency of occurrence in different age categories and neuropathological diagnostic criteria. J Neural Transm 1998;105:801-19.

Braak H, Braak E. Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. Neurosci Lett. 1987;76:124-7.

Brunnström HR, Englund EM. Cause of death in patients with dementia disorders. Eur J Neurol. 2009;16:488-92.

Cercy SP, Bylsma FW. Lewy bodies and progressive dementia: a critical review and meta-analysis. J Int Neuropsychol Soc. 1997;3:179-94.

Chamandy N, Wolfson C. Underlying cause of death in demented and non-demented elderly Canadians. Neuroepidemiology. 2005;25:75-84.

Doody R, Pavlik V, Massman P, Kenan M, Yeh S, Powell S, Cooke N, Dyer C, Demirovic J, Waring S, Chan W. Changing patient characteristics and survival experience in an Alzheimer's center patient cohort. Dement Geriatr Cogn Disord. 2005;20:198-208.

Dyer C. The interaction of ageing and lung disease. Chron Respir Dis. 2012;9:63-7.

El-Solh AA, Sikka P, Ramadan F, Davies J. Etiology of severe pneumonia in the very elderly. Med Clin North Am. 1994;78:1015-33.

Fein AM. Pneumonia in the elderly. Special diagnostic and therapeutic considerations. Med Clin North Am. 1994;78:1015-33.

Feinberg MJ, Ekberg O, Segall L, Tully J. Deglutition in elderly patients with dementia: findings of videofluorographic evaluation and impact on staging and management. Radiology. 1992;183:811-4.

Feldman HH, Pirttila T, Dartigues JF, Everitt B, Van Baelen B, Brashear HR, Berlin JA, Battisti WP, Kavanagh S. Analyses of mortality risk in patients with dementia treated with galantamine. Acta Neurol Scand. 2009;119:22-31.

Fernández M, Gobartt AL, Balañá M; COOPERA Study Group. Behavioural symptoms in patients with Alzheimer's disease and their association with cognitive

impairment. BMC Neurol. 2010;10:87.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112-7.

Foley NC, Affoo RH, Martin RE. A systematic review and meta-analysis examining pneumonia-associated mortality in dementia. Dement Geriatr Cogn Disord. 2015;39:52-67.

Fu C, Chute DJ, Farag ES, Garakian J, Cummings JL, Vinters HV. Comorbidity in Dementia: An autopsy Study. Arch Pathol Lab Med. 2004;128:32-8.

Fukuyama H, Yamashiro S, Tamaki H, Kishaba T. A prospective comparison of nursing- and healthcare-associated pneumonia (NHCAP) with community-acquired pneumonia (CAP). J Infect Chemother.2013;19:719-26.

Golbe LI. Progressive supranuclear palsy. Semin Neurol. 2014;34:151-9.

Goldberg LS, Altman KW. The role of gastrostomy tube placement in advanced dementia with dysphagia: a critical review. Clin Interv Aging. 2014:1733-9.

Guo X, Waern M, Sjögren K, Lissner L, Bengtsson C, Björkelund C, Ostling S, Gustafson D, Skoog I. Midlife respiratory function and Incidence of Alzheimer's

disease: a 29-year longitudinal study in women. Neurobiol Aging. 2007;28:343-50.

Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013;80:1778–1783.

Helmes E, Bowler JV, Merskey H, MunozDG, Hachinski VC. Rates of cognitive decline in Alzheimer's disease and dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2003;15:67-71.

Helmes E, Bowler JV, Merskey H, MunozDG, Hachinski VC. Rates of cognitive decline in Alzheimer's disease and dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2003;15:67-71.

Helmes E, Bowler JV, Merskey H, MunozDG, Hachinski VC. Rates of cognitive decline in Alzheimer's disease and dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2003;15:67-71.

Hishikawa N, Hashizume Y, Yoshida M, Sobue G. Clinical and neuropathological correlates of Lewy body disease. Acta Neuropathol.2003;105:341-50.

Horimoto Y, Matsumoto M, Akatsu H, Ikari H, Kojima K, Yamamoto T, Otsuka Y, Ojika K, Ueda R, Kosaka K. Autonomic dysfunctions in dementia with Lewy bodies. J Neurol. 2003;250:530-3.

Ikejima C, Hisanaga A, Meguro K, Yamada T, Ouma S, Kawamuro Y, Hyouki K, Nakashima K, Wada K, Yamada S, Watanabe I, Kakuma T, Aoyama Y, Mizukami K, Asada T. Multicentre population-based dementia prevalence survey in Japan: a preliminary report. Psychogeriatrics. 2012;12:120-3.

Ikejima C, Ikeda M, Hashimoto M, Ogawa Y, Tanimukai S, Kashibayashi T, Miyanaga K, Yonemura K, Kakuma T, Murotani K, Asada T. Multicenter population-based study on the prevalence of early onset dementia in Japan: vascular dementia as its prominent cause. Psychiatry Clin Neurosci. 2014;68:216-24.

Inagaki T, Yamamoto T, Nokura K, Hashizume Y, Niimi T, Hasegawa R, Ojika K, Yamamoto M. Five year follow-up study on dementia in institutions for the elderly. Nihon Ronen Igakkai Zasshi. 1992;29:729-34. (Japanese)

Janssens JP, Krause KH. Pneumonia in the very old. Lancet Infect Dis. 2004;4:112-24.

Jellinger KA. Prevalence of vascular lesions in dementia with Lewy bodies. A postmortem study. J Neural Transm. 2003;110:771-8.

Jeon YK, Shin MJ, Kim MH, Mok JH, Kim SS, Kim BH, Kim SJ, Kim YK, Chang JH, Shin YB, Kim IJ. Low pulmonary function is related with a high risk of sarcopenia in community-dwelling older adults: the Korea National Health and

Nutrition Examination Survey (KNHANES) 2008-2011. Osteoporos Int. 2015;26:2423-9.

Kammoun S, Gold G, Bouras C, Giannakopoulos P, McGee W, Herrmann F, Michel JP. Immediate causes of death of demented and non-demented elderly. Acta Neurol Scand Suppl. 2000;176:96-9.

Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R, Linde-Zwirble WT. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med 2002;165:766-72.

Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, Linde-Zwirble WT, Angus DC. Pneumonia: still the old man's friend? Arch Intern Med. 2003;163:317-23.

Kosaka K, Iseki E, Arai H. Recent advances in dementia research in Japan: Alzheimer-type dementia. Psychiatry Clin Neurosci. 1999;53:1-10.

Kosaka K, Matsushita M, Oyanagi S, Mehraein P. A cliniconeurophathological study of the "Lewy body disease". Phychiat Neurol Jap 1980;82:292-311. (Japanese)

Kosaka K, Oyanagi S, Matsushita M, Hori A. Presenile dementia with Alzheimer-, Pick- and Lewy-body changes. Acta Neuropathol. 1976;15:221-33.

Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease? Clin Neuropathol. 1984;3:185-92.

Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease? Clin Neuropathol. 1984;3:185-92.

Kosaka K. Diffuse Lewy body disease in Japan. J Neurol. 1990;237:197-204.

Kua EH, Ho E, Tan HH, Tsoi C, Thng C, Mahendran R. The natural history of dementia. Psychogeriatrics. 2014;14:196-201.

Kukull WA, Brenner DE, Speck CE, Nochlin D, Bowen J, McCormick W, et al. Causes of death associated with Alzheimer disease: variation by level of cognitive impairment before death. J Am Geriatr Soc. 1994;42:723-6.

Lai EC, Wong MB, Iwata I, Zhang Y, Hsieh CY, Kao Yang YH, Setoguchi S. Risk of pneumonia in new users of cholinesterase inhibitors for dementia. J Am Geriatr Soc. 2015;63:869-76.

Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA. 2004;292:2901-8.

Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, Kukull WA.

Survival after initial diagnosis of Alzheimer disease. Ann Intern Med. 2004;140:501-9.

Laukkanen P, Heikkinen E, Kauppinen M. Muscle strength and mobility as predictors of survival in 75-84-year-old people. Age Ageing. 1995;24:468-73.

Leroy O, Vandenbussche C, Coffinier C, Bosquet C, Georges H, Guery B, Thevenin D, Beaucaire G. Community-acquired aspiration pneumonia in intensive care units. Epidemiological and prognosis data. 1997;156:1922-9.

Liao KM, Lin TC, Li CY, Yang YH. Dementia Increases Severe Sepsis and Mortality in Hospitalized Patients With Chronic Obstructive Pulmonary Disease. Medicine (Baltimore) 2015;94:e967. doi: 10.1097/MD.0000000000000967.

Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Neurologic Diseases in the Elderly Research Group. Prevalence of dementia and major subtypes in Europe: A collaboration study of population-based cohorts. Neurology. 2000;54: S4–9.

Loeb M, McGeer A, McArthur M, Walter S, Simor AE. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. Arch Intern Med 1999;159:2058-64.

Londos E, Hanxsson O, Alm Hirsch I, Janneskog A, Bülow M, Palmqvist S. Dysphagia in Lewy body dementia - a clinical observational study of swallowing function by videofluoroscopic examination. BMC Neurol. 2013;13:140. doi: 10.1186/1471-2377-13-140.

Lopez OL, Becker JT, Kaufer DI, Hamilton RL, Sweet RA, Klunk W, DeKosky ST. Research evaluation and prospective diagnosis of dementia with Lewy bodies. Arch Neurol. 2002;59:43-6.

Lopez OL, Wisniewski S, Hamilton RL, Becker JT, Kaufer DI, DeKosky ST. Predictors of progression in patients with AD and Lewy bodies. Neurology. 2000;54:1774-9.

Magaki S, Yong WH, Khanlou N, Tung S, Vinters HV. Comorbidity in dementia: update of an ongoing autopsy study. J Am Geriatr Soc 2014;62:1722-1728.

Manabe T, Mizukami K, Akatsu H, Teramoto S, Yamaoka Y, Nakamura S, Ohkubo T, Kudo K, Hizawa N. Influence of pneumonia complications on the prognosis of patients with autopsy-confirmed Alzheimer's disease, dementia with Lewy bodies, and vascular dementia. Psychogeriatrics. 2016;16:305-14.

Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk Factors for Aspiration Pneumonia in Older Adults. PLoS One. 2015;10:e0140060. doi: 10.1371/journal.pone.0140060. eCollection 2015.

Marengoni A, Corrao S, Nobili A, Tettamanti M, Pasina L, Salerno F, Iorio A, Marcucci M, Bonometti F, Mannucci PM; SIMI Investigators. In-hospital death according to dementia diagnosis in acutely ill elderly patients: the REPOSI study. Int J Geriatr Psychiatry. 2011;26:930-6.

Marrie TJ. Epidemiology of community-aquired pneumonia in the elderly. Semin Respir Infect 1990;5:260-8.

Matsui Y, Tanizaki Y, Arima H, Yonemoto K, Doi Y, Ninomiya T, Sasaki K, Iida M, Iwaki T, Kanba S, Kiyohara Y. Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama study. J Neurol Neurosurg Psychiatry. 2009;80:366-70.

McKeith IG, Ballard CG, Perry RH, Ince PG, O'Brien JT, Neill D, Lowery K, Jaros E, Barber R, Thompson P, Swann A, Fairbairn AF, Perry EK. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology. 2000;54:1050-8.

McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien J, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA,

Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65:1863-72.

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113-1124.

McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis. 2006;9(3 Suppl):417-23.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34:939-44.

Meguro K, Ishii H, Yamaguchi S, et al. Prevalence of dementia and dementing diseases in Japan: the Tajiri project. Arch Neurol. 2002;59:1109-14.

Ministry of Health, Labour and Welfare - Japan. The current condition of dementia. 2012. Avialable at www.mhlw.go.jp/file/05-Shingikai.../0000065682.pdf.

Ministry of Health, Labour and Welfare - Japan. Vital statistics of Japan. Available at http://www.mhlw.go.jp/toukei/list/81-1a.html.

Mizukami K, Homma T, Aonuma K, Kinoshita T, Kosaka K, Asada T. Decreased ventilatory response to hypercapnia in dementia with Lewy bodies. Ann Neurol. 2009;65:614-7.

Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med. 2005;6:347–352.

Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. Am J Med 1998;105:319-30.

Mölsä PK, Marttila RJ, Rinne UK. Survival and cause of death in Alzheimer's disease and multi-infarct dementia. Acta Neurol Scand. 1986;74:103-7.

Nogami A, Yamazaki M, Saito Y, Hatsuta H, Sakiyama Y, Takao M, Kimura K, Murayama S. Early Stage of Progressive Supranuclear Palsy: A

Neuropathological Study of 324 Consecutive Autopsy Cases. J Nippon Med Sch. 2015;82:266-73.

Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, Katzman R, Thal LJ. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology. 1998;51:351-7.

Ostbye T, Hill G, Steenhuis R. Mortality in elderly Canadians with and without dementia: a 5-year follow-up. Neurology. 1999;53:521-6.

Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, Hofman A. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ. 1995:15;310(6985):970-3.

Pathan SS, Gottesman RF, Mosley TH, Knopman DS, Sharrett AR, Alonso A. Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities (ARIC) Study. Eur J Neurol. 2011;18:888-98.

Perry RH, Irving D, Blessed G, Fairbairn A, Perry EK. Senile dementia of Lewy body type. A clinically and neuropathologically distinct form of Lewy body dementia in the elderly. J Neurol Sci. 1990;95:119-39.

Pistacchi M, Gioulis M, Contin F, Sanson F, Marsala SZ. Sleep disturbance and

cognitive disorder: epidemiological analysis in a cohort of 263 patients. Neurol Sci. 2014;35:1955–1962.

Polverino E, Torres A, Menendez R, Cilloniz C, Valles JM, Capelastegui A, Marcos MA, Alfageme I, Zalacain R, Almirall J, Molinos L, Bello S, Rodríguez F, Blanquer J, Dorado A, Llevat N, Rello J; HCAP Study investigators. Microbial aetiology of healthcare associated pneumonia in Spain: a prospective, multicentre, case-control study. Thorax 2013;68:1007-14.

Rankin K. P., Baldwin E., Pace-Savitsky C., Kramer J. H., Miller B. L. Self awareness and personality change in dementia. J. Neurol. Neurosur. Psychiatry 2005;76: 632–639.

Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250-60.

Román GC. Vascular dementia may be the most common form of dementia in the elderly. J Neurol Sci. 2002;203-204:7-10.

Russ TC, Starr JM, Stamatakis E, Kivimäki M, Batty GD. Pulmonary function as a risk factor for dementia death: an individual participant meta-analysis of six UK

general population cohort studies. J Epidemiol Community Health. 2015;69:550-6.

Rösler A, Pfeil S, Lessmann H, Höder J, Befahr A, von Renteln-Kruse W. Dysphagia in Dementia: Influence of Dementia Severity and Food Texture on the Prevalence of Aspiration and Latency to Swallow in Hospitalized Geriatric Patients. J Am Med Dir Assoc. 2015;16:697-701.

Seelaar H., Rohrer J. D., Pijnenburg Y. A., Fox N. C., van Swieten J. C. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J. Neurol. Neurosurg. Psychiatry. 2011;82:476–486.

Shinagawa S, Adachi H, Toyota Y, Mori T, Matsumoto I, Fukuhara R, Ikeda M. Characteristics of eating and swallowing problems in patients who have dementia with Lewy bodies. Int Psychogeriatr. 2009;21:520-5.

Snowden JS, Thompson JC, Stopford CL, et al. The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. Brain. 2011;134(Pt 9):2478-92.

Stavitsky K, Brickman AM, Scarmeas N, The progression of cognition, psychiatric symptoms, and functional abilities in dementia with Lewy bodies and Alzheimer

disease. Arch Neurol. 2006;63(10):1450-6.

Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. PLoS One. 7:e45451, 2012. doi: 10.1371/journal.pone.0045451.

Stubendorff K, Hansson O, Minthon L, Londos E. Differences in survival between patients with dementia with Lewy bodies and patients with Alzheimer's disease--measured from a fixed cognitive level. Dement Geriatr Cogn Disord. 2011;32(6):408-16.

Suh MK, Kim H, Na DL. Dysphagia in patients with dementia: Alzheimer versus vascular. Alzheimer Dis Assoc Disord. 2009;23(2):178-84.

Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. Am J Med. 2013;126:995-1001.

Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T; Japanese Study Group on Aspiration Pulmonary Disease. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc 2008;56:577-9.

Teramoto S, Fukuchi Y. Detection of aspiration and swallowing disorder in older stroke patients: simple swallowing provocation test versus water swallowing test. 2000;81:1517-9.

Teramoto S, Matsuse T, Fukuchi Y, Ouchi Y. Simple two-step swallowing provocation test for elderly patients with aspiration pneumonia. Lancet. 1999;353:1243.

The World Health Organization. 10 fact on dementia. Available at http://www.who.int/features/factfiles/dementia/en/

The World Health Organization. Dementia Fact sheet No. 362. 2015. Available at http://www.who.int/mediacentre/factsheets/fs362/en/#

The committee for the Japanese Respiratory Society guidelines in management of respiratory infections. The Japanese Respiratory Society guideline for the management of community-acquired pneumonia in adults. Respirology 2006;11: S1-S133.

The committee for the Japanese Respiratory Society guidelines in management of respiratory infections. The Japanese Respiratory Society guideline for the management of hospital-acquired pneumonia in adults 2008. Respirology 2009;14: S1-S71.

Todd S, Barr S, Passmore AP. Cause of death in Alzheimer's disease: a cohort study.

QJM. 2013;106:747-53.

Togo T, Isojima D, Akatsu H, Suzuki K, Uchikado H, Katsuse O, Iseki E, Kosaka K, Hirayasu Y. Clinical features of argyrophilic grain disease: a retrospective survey of cases with neuropsychiatric symptoms. Am J Geriatr Psychiatry. 2005;13:1083-91.

Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. Exp Neurol. 2015;272:97-108.

Vidal JS, Aspelund T, Jonsdottir MK, et al. Pulmonary function impairment may be an early risk factor for late-life cognitive impairment. J Am Geriatr Soc. 2013;61:79-83.

World Health Organization. Dementia Fact sheet N^{o} 362. March 2015. Available at http://www.who.int/mediacentre/factsheets/fs362/en/

Wada H, Nakajoh K, Satoh-Nakagawa T, Suzuki T, Ohrui T, Arai H, Sasaki H. Risk factors of aspiration pneumonia in Alzheimer's disease patients. Gerontology. 2001;47:271-6.

Walker A. J., Meares S., Sachdev P. S., Brodaty H. The differentiation of mild frontotemporal dementia from Alzheimer’s disease and healthy aging by neuropsychological tests. Int. Psychogeriatr. 2005;17:57–68.

Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology. 2006;67:1935-41.

Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology. 2006;67:1935-41.

Writing committee of the Guideline for Dementia, Japanese Society of Neurology. The Guideline for Dementia 2010. Tokyo, Igakusyoin, 2010.

Yamamoto T, Kobayashi Y, Murata M. Risk of pneumonia onset and discontinuation of oral intake following videofluorography in patients with Lewy body disease. Parkinsonism Relat Disord. 2010;16:503-6.

Yoshita M, Arai H, Arai H, Arai T, Asada T, Fujishiro H, Hanyu H, Iizuka O, Iseki E, Kashihara K, Kosaka K, Maruno H, Mizukami K, Mizuno Y, Mori E, Nakajima K, Nakamura H, Nakano S, Nakashima K, Nishio Y, Orimo S, Samuraki M, Takahashi A, Taki J, Tokuda T, Urakami K, Utsumi K, Wada K, Washimi Y, Yamasaki J, Yamashina S, Yamada M. Diagnostic accuracy of 123I-meta-iodobenzylguanidine myocardial scintigraphy in dementia with Lewy bodies: a multicenter study. PLoS One. 2015;10:e0120540. doi:

10.1371/journal.pone.0120540. eCollection 2015.

厚生労働省労健局高齢者支援課　認知症・虐待防止対策室. 認知症施策の現状.

平成 25 年 12 月 19 日.

TABLES and FIGURES

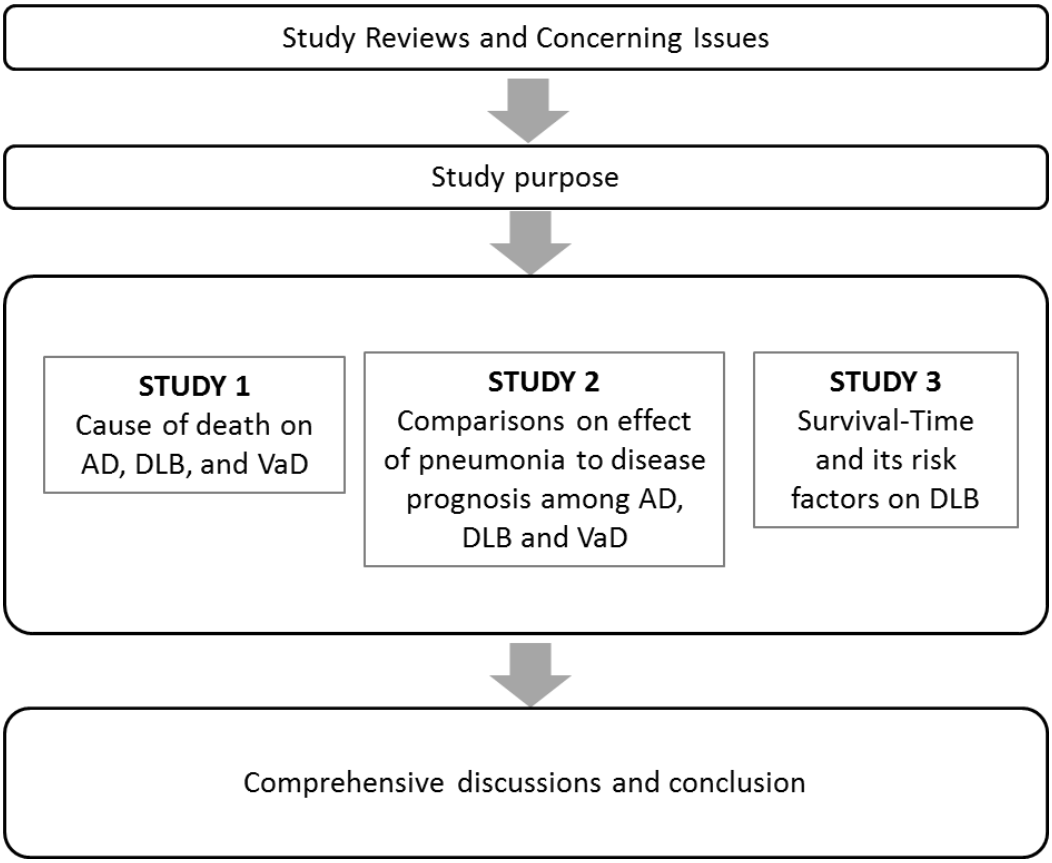

Fig. 1-1 Framework of the study

Table 2-1. Frequency of pneumonia-associated mortality on patients with dementia among reviewed studies

Information resources	Study, published year	country	Patients	Age at death, mean±SD-yr.	Frequency of pneumonia-associated mortality on dementia	
					Underlying cause of death	Immediate cause of death
Death Certificate	Todd S 2013	USA	396 (202 AD)	78.6 ± 7.5 (at entry)	15%	-
	Chamandy and Wolfson 2005	Canada	823	87.8 ± 7.26	12.3%	-
	Ganguli 2005	USA	1681 (348 AD)	73.4±5.9 (at entry)	12.3%	-
	Tschanz 2004	Sweden	355	83.3 ± 7.0	13% (AD 11%, VaD 13%, AD/VaD 18%)	
	Beard 1996	USA	959 AD	-	4.4%	26.6%
	Kukull 1994	USA	105 (55 AD)	82.5	10.3%	-
Both	Burns 1990	UK	178 AD	80.4 (56-99)	Death certificate・・・・・・67.9% Autopsy・・・・・・・・・・64.0%	
Autopsy	Magaki S 2014	USA	218	77.6 ± 8.9	66.3% AD 68.9%	-
	Brunnstrom 2009	Sweden	524	78 ± 9.1	Bronchopenuminia, 38.4% Aspiration pneumonia, 6.7% (AD: BP, 47.3%; AP, 7.7%) (VaD: BP, 27.4%; AP, 4.8%)	
	Attems 2005	Austria	308	83.5 ± 8.6	45.5% (AD 49.6%, VaD 33.3%)	
	Fu 2004	USA	202	77.6 ± 10.8	46.2% (AD 41.3%)	
	Kammoun 2000	Switzerland	342 (120 AD, VaD and Mixed))	85.0 ± 6.9	-	40.8%

AD, Alzheimer's Disease; VaD, Vascular dementia; BP, bronchopneumonia; AP, aspiration pneumonia

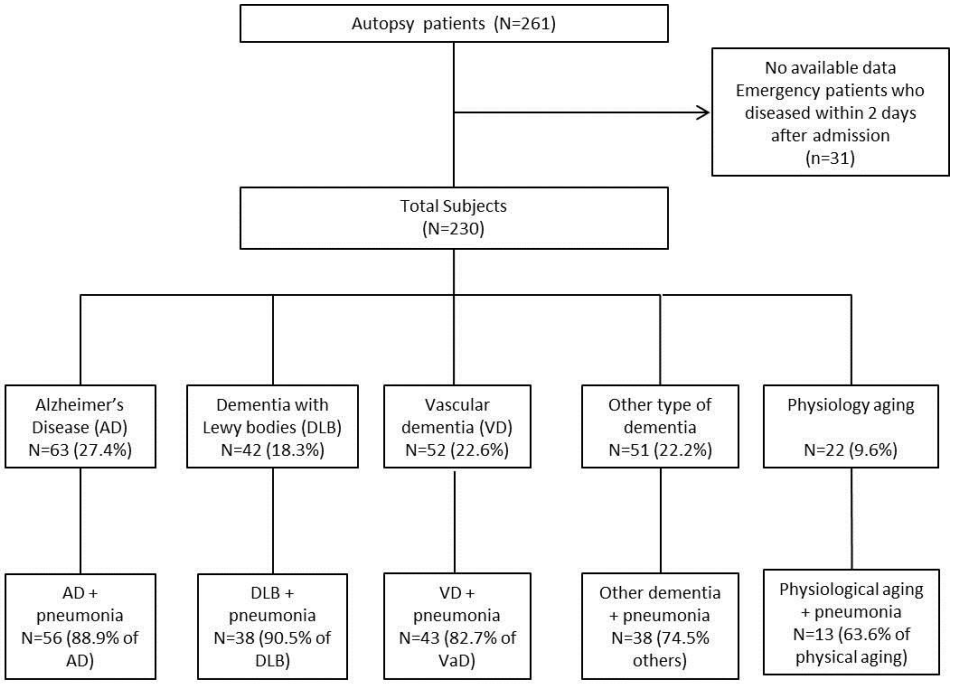

Fig. 3-1 Study population

A total of 261 patients died and were autopsied at the study site during the observational period. After excluding the patients who died within 1 week of an emergency visit to the hospital and who did not have data available, the total 157 patients were determined Alzheimer's disease, dementia with Lewy bodies, and vascular dementia by neuropathological diagnoses and were eligible to the present study.

Table 3-1. General characteristics of patients with Alzheimer's disease, dementia with Lewy bodies, or vascular dementia

n=157

	AD N=63	**DLB** N=42	**VaD** N=52	**P value**
Complication of pneumonia	56 (88.9)	38 (90.5)	43 (82.7)	0.306[1]
Gender - n (%)				0.010[1]
Male	20 (31.7)	12 (28.6)	27 (51.9)	
Female	43 (68.3)	30 (71.4)	25 (48.1)	
Age				
Time of dementia onset – median (IQR), yr.	79 (72-84)	78 (72-84)	76 (70-82)	0.269[3]
<65	8 (12.7)	4 (9.5)	6 (11.5)	0.125[1]
65 – 74	11 (17.5)	9 (21.4)	17 (32.7)	
≥ 75	44 (69.8)	29(69.0)	29 (55.8)	
Clinical characteristics				
BMI at admission- median (IQR) (n=77)	19 (16-20)	18 (14-21)	19 (18-22)	0.096[3]
Weightof brain - median (IQR) (n=135)	1047 (980-1170)	1050 (1000-1140)	1080 (982-1153)	0.062[3]
Pathological findings				
Cerebral infarction	27 (42.9)	15 (35.7)	43 (82.7)	<0.001[1]
Comorbidities– n (%)				
Hypertension	27 (42.9)	11 (26.2)	31 (59.6)	0.001[1]
Pulmonary emphysema	11 (17.5)	8 (19.0)	10 (19.2)	0.853[1]
Diabetes mellitus	10 (15.9)	2 (4.8)	14 (26.9)	0.007[1]
Angina	5 (8.1)	3 (6.5)	3 (6.5)	0.801[2]
Heartfailure	5 (8.1)	2 (4.3)	2 (3.8)	0.507[2]
Malignant neoplasm	10 (16.1)	2 (4.3)	4 (7.7)	0.047[1]
Events after admission– n (%)				
PEG	19 (30.2)	17 (40.5)	25 (48.1)	0.046[1]
Urinary tract infection	10 (16.1)	9 (19.6)	8 (15.4)	0.521[1]
Swallowing dysfunctions – n (%)	26 (41.3)	23 (54.8)	23 (44.2)	0.157[1]
Medications – n (%)				
Anti-dementia drug*	12 (19.4)	3 (6.5)	2 (3.8)	0.007[1]
Benzodiazepines use	6 (9.7)	9 (19.6)	7 (13.5)	0.143[1]

AD, Alzheimer's disease; DLB, dementia with Lewy Bodies; VaD, vascular dementia; PEG, percutaneous endoscopic gastrostomy; IQR, **interquartile range**

*Anti-dementia drug included acetylcholine inhibitors and NMDA receptor inhibitor

[1]Chi-squire test, [2]Fisher's exact test, [3]Kruskal-Wallis test

Table 3-2. Immediate and underlying cause of death in dementia patients with and without pneumonia

n=157

	AD N=63	DLB N=42	VaD N=52	P value
Underlying cause of death				
Pneumonia	31 (49.2)	9 (21.4)	15 (28.8)	0.001[1]
Cerebrovascular accident	6 (9.7)	3 (7.1)	6 (11.5)	0.405[2]
Heart failure	9 (14.5)	13 (28.3)	6 (11.5)	0.006[1]
Respiratory failure	1 (1.6)	1 (2.2)	2 (3.8)	1.000[2]
Renal failure	1 (1.6)	2 (4.3)	5 (9.6)	0.051[1]
Failureon liver, gallbladder, pancreas	2 (3.2)	2 (4.3)	1 (1.9)	1.000[2]
Diabe1tes mellitus	1 (1.6)	3 (6.5)	0 (0.0)	0.101[1]
Malignant neoplasm	5 (8.1)	6 (13.0)	6 (11.5)	0.274[1]
Sepsis	3 (4.8)	3 (6.5)	7 (13.5)	0.061[1]
Geromarasmus	1 (1.6)	1 (2.2)	0 (1.3)	1.000[2]
Sudden unexpected natural death	0 (0.0)	1 (2.2)	0 (0.0)	0.268[2]
Seizure	0 (0.0)	0 (0.0)	2 (3.8)	1.000[2]
Others	3 (4.8)	2 (4.3)	2 (3.8)	0.967[1]
Immediate cause of death				
Pneumonia	33 (52.4)	22 (52.4)	15 (28.8)	0.007[1]
Cerebrovascular accident	5 (8.1)	1 (2.2)	4 (7.7)	0.188[1]
Heart failure	5 (7.9)	1 (2.4)	4 (7.7)	1.000[2]
Respiratory failure	2 (3.2)	5 (10.9)	6 (11.5)	0.053[1]
Renal failure	5 (8.1)	6 (13.0)	11 (21.2)	0.046[1]
Failure on liver, gallbladder, pancreas	2 (3.2)	0 (0.0)	0 (0.0)	1.000[2]
Malignant neoplasm	6 (9.7)	0 (0.0)	4 (7.7)	1.000[2]
Sepsis	4 (6.5)	3 (6.5)	6 (11.5)	0.228[1]
Sudden unexpected natural death	0 (0.0)	3 (7.1)	0 (0.0)	0.610[2]
Seizure	1 (1.6)	0 (0.0)	1 (1.9)	1.000[2]
Others	4 (6.5)	2 (4.3)	3 (5.8)	0.791[1]

AD, Alzheimer's disease; DLB, Dementia with Lewy Bodies; VaD, Vascular Dementia

[1]Chi-squire test, [2]Fisher's exact test

Table 4-1. Clinical time course of dementia patients with AD, DLB, and VaD

n=157

	AD N=63	**DLB** N=42	**VaD** N=52	**P value***
Age of dementia onset	79 (72-84)	78 (72-84)	76 (70-82)	0.269
Age of death	86 (82-92)	87 (81-92)	83 (78-87)	0.018
Total years (from onset to death)	8 (5-13)	8 (5-15)	5 (3-9)	0.015
According to pneumonia complication				
with pneumonia (n=137)	8 (5-13)	8 (5-14)	5 (3-8)	0.006
without pneumonia (n=20)	7 (3-12)	13 (5-18)	5 (3-12)	0.181
According to groups of dementia onset age				<0.001
＜65yr. (n=17)	17 (13-22)	16 (15-19)	7 (3-11)	
65 - 74 (n=36)	11 (8-13)	12 (8-16)	7 (4-12)	
≥75yr. (n=102)	6 (4-10)	6 (4-10)	5 (3-6)	
Years between dementia onset to admission	6 (2-8)	5 (3-8)	3 (1-6)	0.015
Years between hospital admission to death	2 (1-5)	3 (1-8)	3 (1-5)	0.404

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; VaD, vascular dementia

Time course on each variable was presented by median (**interquartile range**), years.

*Kruskal-Wallis test

Table 4-2. Risk factors for time to mortality from dementia onset in dementia patients using Cox proportional hazard model

	HR	95% CI	P value
Gender-male	1.942	1.362-2.769	<0.001
Pneumonia	1.528	0.935-2.496	0.091
Diabetes mellitus	1.585	1.017-2.470	0.042
Age of dementia onset - less than 65 yr.	0.372	0.189-0.734	0.004
Age of dementia onset - 75 yr. and over	2.266	1.507-3.408	0.000
Vascular dementia	2.041	1.397-2.982	0.000

n=157

HR, hazard ratio; CI, confidence interval. *p* value: chi-squire test

Baseline adjustment covariates: gender, pneumonia complication, subtypes of dementia (Alzheimer's disease, dementia with Lewy bodies, Vascular dementia), groups of onset age (<65yr., 65-74yr., ≥75yr.), pneumonia complication, comorbidities (hypertension, diabetes mellitus, heart failure, cerebral infarction, pulmonary emphysema, angina, malignant neoplasm), swallowing dysfunction, urinary tract infection, and percutaneous endoscopic gastrostomy. Presented items of $p<0.1$.

The interaction of pneumonia vs. subtypes of dementia was not significant (p=0.340).

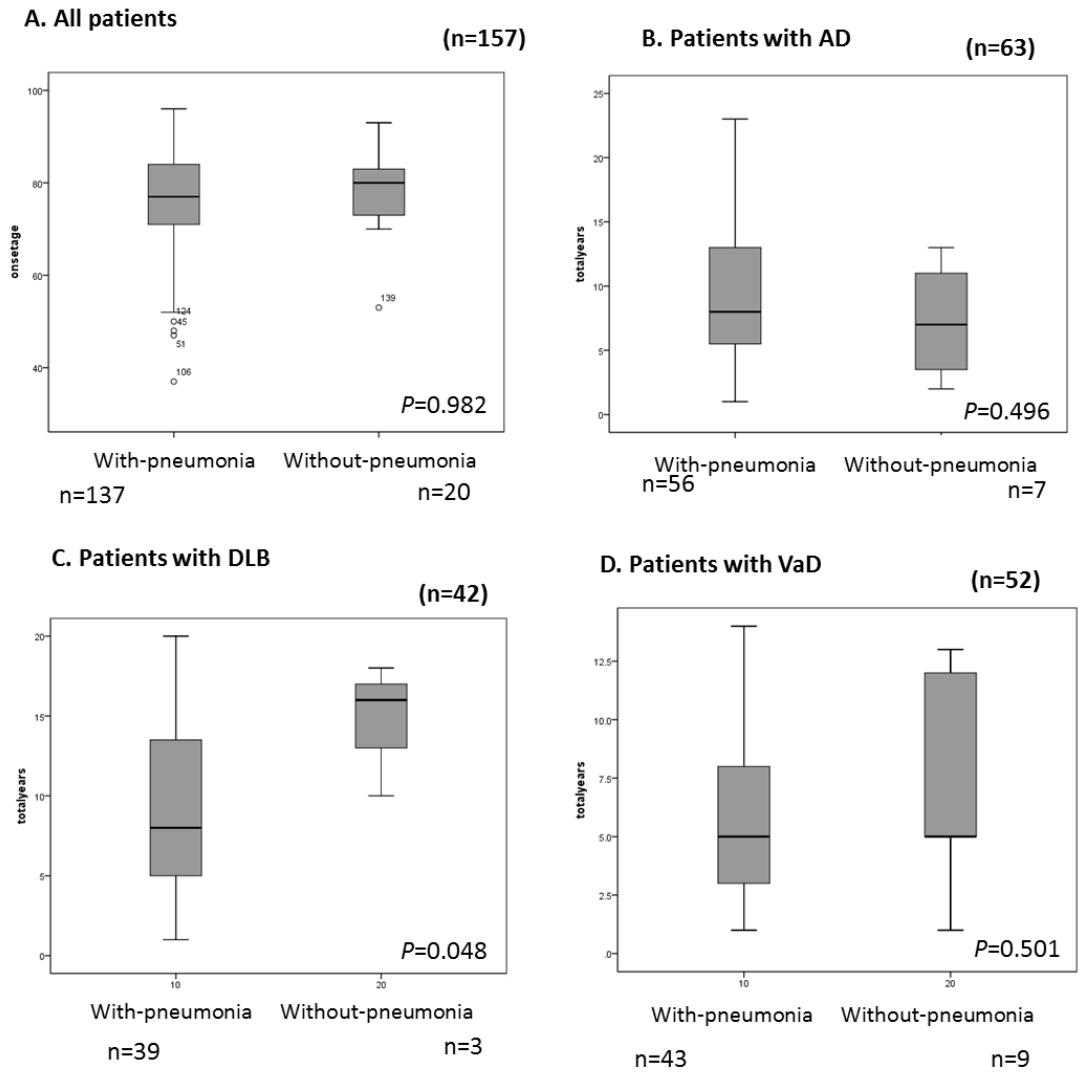

Figure 4-2. Comparisons on survival-time between with- and without-pneumonia. (A), on all eligible patients with dementia (B), on patients with Alzheimer's diseases, (C) on patients with dementia with Lewy bodies, (D) and on patients with Vascular dementia. *P* value was tested by Mann-Whitney U test.

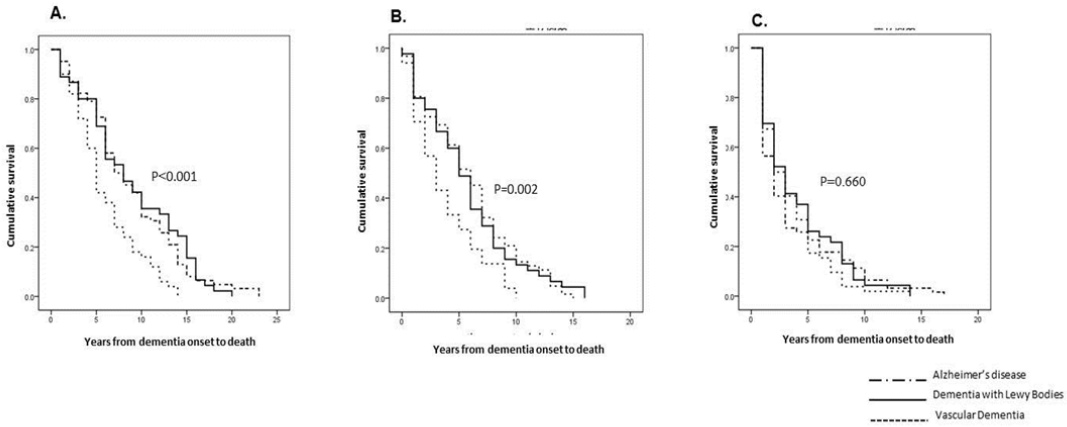

Figure 4-2. Kaplan-Meier curves on the number of years to death from the dementia onset on total dementia patients (A), on the dementia patients with pneumonia (B), and on the dementia patients without pneumonia according to subtypes of dementia. There were significant differences on total patients (log rank test, $p<0.001$) and on patients with pneumonia (log rank test, $p=0.002$), but on patients without pneumonia (log-rank test, $p=0.660$).

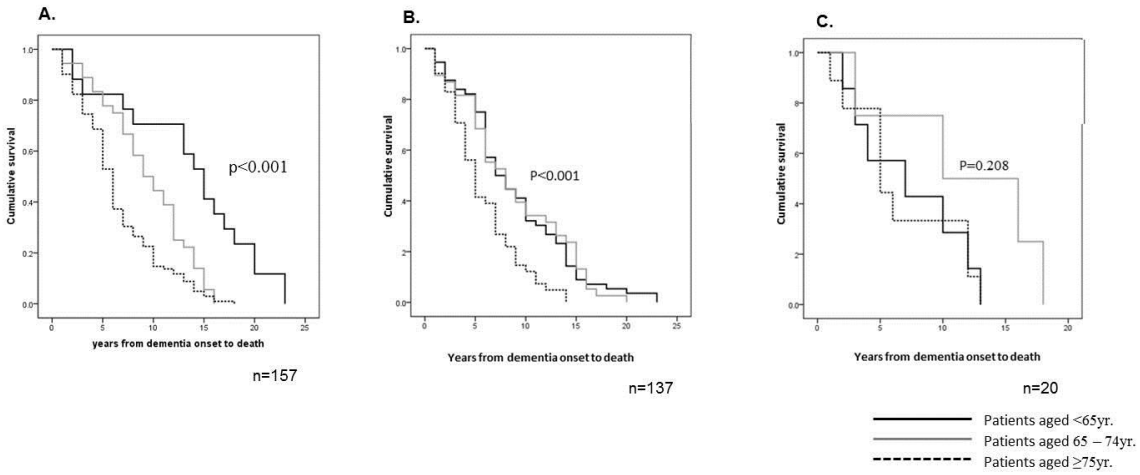

Figure 4-3. Kaplan-Meier curves on the number of years to death from the dementia onset on total dementia patients (A), on the dementia patients with pneumonia (B), and on the dementia patients without pneumonia according to patients on age groups: <65yr; 65 – 74yr; and ≥75yr. There were significant differences on total patients (log-rank test, $p<0.001$) and on patients withpneumonia (log-rank test, $p<0.001$), but on patients without pneumonia (log-rank test, $p=0.208$) with small number of patients.

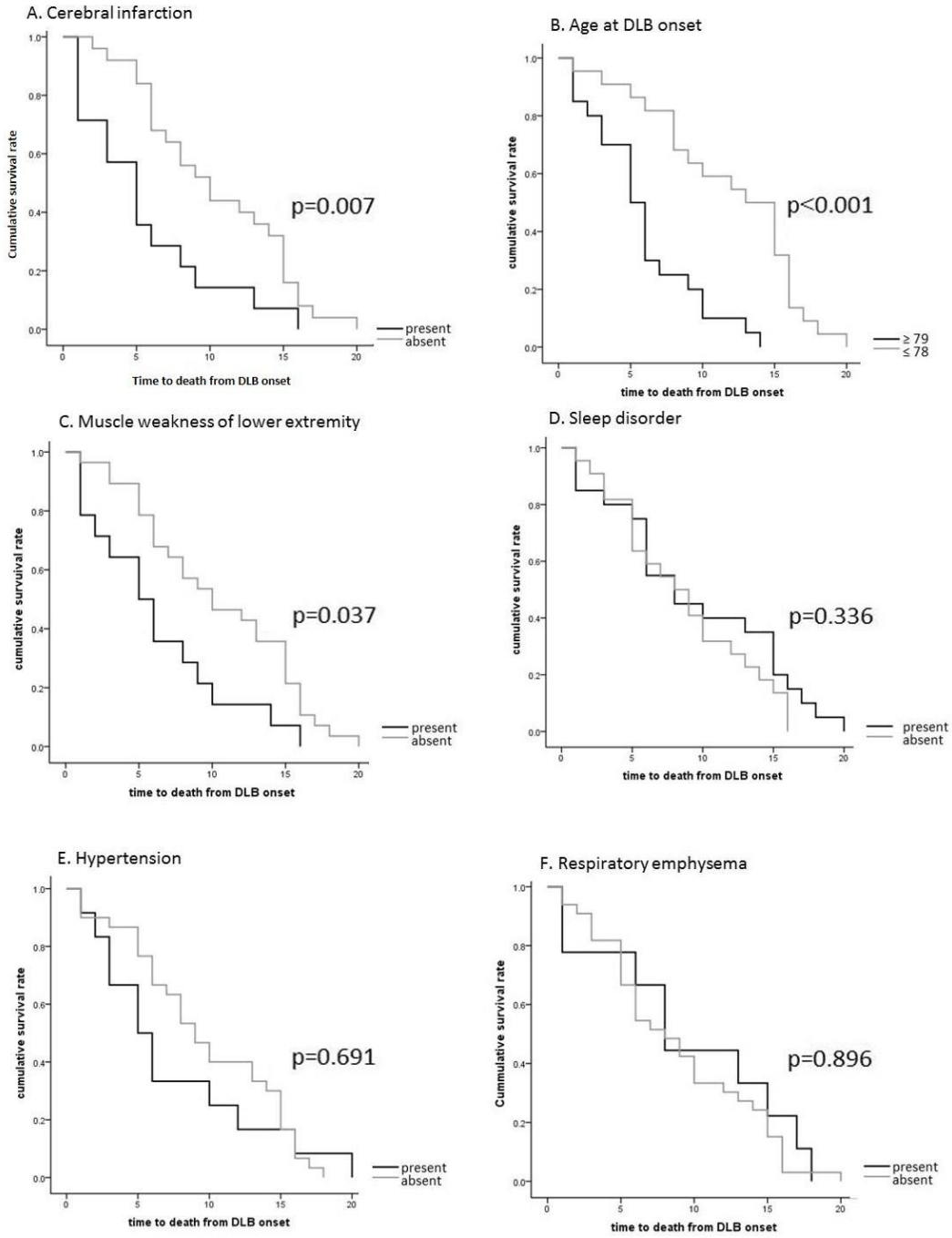

Fig. 5-1 Kaplan-Meier curves on the number of years to death from the onset of dementia with Lewy bodies. Comparisons of each covariance were tested by the log-rank test.

Table 5-1. General characteristics of patients with dementia with Lewy bodies

n=42

	Total - n (%)
Sex - n (%)	
Male	12 (28.6)
Female	30 (71.4)
Age - median (IQR)	
Time of death	87 (81-92)
Time of dementia onset	78 (72-85)
Incidence of pneumonia	39 (92.9)
Neuropathological condition	
Weight of brain - median (IQR) (n=35)	1050 (1000-1140)
Type of DLB	
Limbic	14 (33.3)
Neocortical diffuse	13 (31.0)
Cerebral infarction	15 (35.7)
Clinical condition– n (%)	
BMI at admission- median (IQR) (n=20)	17.8 (13.8-20.8)
Muscle weakness of the lower extremities	14 (33.3)
Increased sputum	12 (28.6)
Swallowing dysfunction	26 (61.9)
PEG	20 (47.6)
Autonomic dysfunction	
Sleep disorder	22 (52.4)
Urinary incontinence	38 (90.5)
Constipation	34 (81.0)
Comorbidity– n (%)	
Hypertension	12 (28.6)
Heart failure	3 (7.1)
Respiratory emphysema	9 (21.4)
Diabetes mellitus	2 (4.8)
Malignant neoplasm	6 (14.3)
Repeated falls	15 (35.7)
Fracture of femur	12 (28.6)
Tuberculosis	3 (7.1)

DLB, Dementia with Lewy Bodies; PEG, Percutaneous Endoscopic Gastrostomy; IQR, **interquartile range**

Table 5-2. Clinical condition among DLB patients with pneumonia

n=39

	Total – n (%)
Age at time of death - median (IQR)	86 (81 - 91)
Male	80 (76 - 87)
Female	88 (85 - 93)
Number of years to death from DLB onset- median, yr. (IQR)	8 (5 - 14)
Male	7 (1 - 15)
Female	8 (5 - 13)
Age of onset ≤78yr.	13 (8 - 16)
Age of onset ≥79yr.	5 (3 - 7)
Immediate cause of death – n (%)	
Pneumonia	21 (53.8)
Respiratory failure	5 (12.8)
Heart failure	1 (2.6)
Sepsis	3 (7.7)
Renal failure	6 (15.4)
Sudden death	4 (10.3)

DLB, Dementia with Lewy Bodies; IQR, **interquartile range**

Table 5-3. Risk factors for survival time of dementia with Lewy bodies by Cox hazard model

	HR	95% CI	*p* value
Sex - Male	2.83	1.24 – 6.50	0.014
Age of onset - ≥78 yr.	4.71	1.82 - 12.18	0.002
Cerebral infarction	2.36	1.12 – 4.96	0.023
Muscle weakness of the lower extremities	2.04	0.95 - 4.39	0.067

n=39

HR, hazard ratio; CI, confidence interval. *p* value: chi-squared test

Baseline adjustment covariates: sex, pneumonia occurrence, pathologically identified cerebral infarction, hypertension, heart failure, malignant neoplasm pulmonary emphysema, fracture of femur, sleep disorder, urinary incontinence, repeated falls, swallowing dysfunction, muscle weakness of the lower extremities, increased sputum, and percutaneous endoscopic gastrostomy. Only items of $p<0.1$ are shown.

Interactions between sex and age of onset, or cerebral infarction and muscle weakness of the lower extremities were not significant ($p=0.712$ or $p=0.449$, respectively).