

Impact of the Severity of Alzheimer's Disease on the Quality of Life, Activities of Daily Living, and Caregiving Costs for Institutionalized Patients on Anti-Alzheimer Medications in Japan

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Abstract.

Background: Alzheimer's disease (AD) increases societal costs and decreases the activities of daily living (ADL) and quality of life (QoL) of the affected individuals.

Objective: We assess the impact of AD severity on ADL, QoL, and caregiving costs in Japanese facilities for the elderly.

Methods: Patients with AD in facilities for the elderly were included (47 facilities, N=3,461). The QoL, ADL, and disease severity of patients were assessed using Barthel Index (BI), EuroQoL-5D-5L (EQ-5D-5L), and Mini-Mental State Examination (MMSE), respectively. Annual caregiving costs were estimated using patients' claims data. The patients were subcategorized into the following three groups according to the MMSE score: mild ($21 \leq \text{MMSE} \leq 30$), moderate ($11 \leq \text{MMSE} \leq 20$), and severe ($0 \leq \text{MMSE} \leq 10$). Changes among the three groups were evaluated using the Jonckheere-Terpstra test.

Results: Four hundred and one participants were on anti-AD medicines, of whom 287 (age: 86.1 ± 6.4 years, 76.7% women) in the mild ($n=53$, 84.0 ± 6.9 years, 71.7%), moderate ($n=118$, 86.6 ± 5.9 years, 76.3%), and severe ($n=116$, 86.6 ± 6.5 years, 79.3%) groups completed the study questionnaires. The mean BI and EQ-5D-5L scores for each group were 83.6, 65.1, and 32.8 and 0.801, 0.662, and 0.436, respectively. The mean annual caregiving costs were 2.111, 2.470, and 2.809 million JPY, respectively. As AD worsened, the BI and EQ-5D-5L scores decreased and annual caregiving costs increased significantly.

Conclusion: AD severity has an impact on QoL, ADL, and caregiving costs.

Keywords: Activities of daily living, Alzheimer's disease, cost of illness, Japan, observational study, quality of life

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INTRODUCTION

Dementia adversely affects mental functions such as thinking and memory as well as daily functioning. It is mainly categorized into four types: Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and others [1]. Patients with dementia are mostly categorized as having AD; the proportion of these patients has been reported to be 60%–80% worldwide and 68% in Japan [2, 3]. The risk factors of AD include age, genetics, and smoking [4, 5].

The world's population is gradually aging. As of 2019, the world's population was estimated to be 7.7 billion, and individuals aged 65 years or higher accounted for approximately 9.1% of this population. By 2030, the world's population is expected to be 8.5 billion and the ≥ 65 -year age group is expected to account for 11.7% of the population [6]. With the increased aging of the global population, the number of patients with AD is increasing. In 2015, there were 46.8 million patients with AD worldwide, and this number is expected to reach 74.7 million in 2030 [7]. Japan has one of the most aged populations in the world. The proportion of aged population is the highest in Japan globally [8]. The proportion of Japanese aged 65 years or higher was 28.4% as of 2019 and is expected to reach 31.2% by 2030 [9]. Consistent with this finding, the number of patients with AD in Japan is expected to increase. This number was 3 million in Japan in 2012 and will reach 5–6 million in 2030 [3, 10, 11].

The societal costs of dementia are increasing, in line with the increase in the number of AD patients in Japan. This cost was 14.5 trillion Japanese yen (JPY) in 2014, of which the caregiving cost was 6.4 trillion JPY and was higher than medical or informal care cost [12]. The long-term care insurance system in Japan is managed by the Ministry of Health, Labour and Welfare. Payment limits for caregiving services are determined by support/care levels. These support/care levels are classified into seven groups: support levels 1 and 2 and care levels 1–5 [13]. One of the most frequent reasons for care level certification in Japan is dementia, which is the number one cause of certifications of care levels 1, 2, and 3 and the second highest cause of those of care levels 4 and 5 [14].

The burden on caregivers increases with the severity of AD [15]. When the severity of AD increases to an extent that it badly affects daily functioning, patients' activities of daily living (ADL) are impaired and they need help from others in managing their daily lives [16, 17]. As the severity of AD increases,

patients' ADL decreases and the burden on caregivers increases [18, 19]. Furthermore, the quality of life (QoL) of both patients and caregivers decreases [20, 21].

A few cross-sectional studies on the relationship between the severity of AD and ADL, QoL, and any cost have been conducted in Japan. One such study investigated the burden on caregivers and QoL of residents in nursing homes [22]. Moreover, there are fewer cohort studies about AD in Japan [3, 23], and to the best of our knowledge, thus far, no cohort study on the relationship between the severity of AD and outcomes such as ADL and QoL has been conducted in Japan. Therefore, in this study, we aimed to evaluate the impact of AD severity on QoL, ADL, and caregiving costs and their changes among facilities for the elderly in Japan.

METHODS

Study design

We enrolled people admitted to nursing homes or residential facilities with health and caregiving services for the elderly under Life Company Limited between March 2019 and March 2020 (47 facilities, $N=3,461$). We focused only on patients who were on prescribed medicines for AD, specifically those who received donepezil, galantamine, rivastigmine, or memantine. Patients' baseline demographic information, such as age, sex, and care level required, were derived from the database managed by Life Company Limited. Patients' QoL, ADL, and severity of dementia were assessed in March 2019 and March 2020 by the staff working at the facilities using the Barthel Index (BI), EuroQoL-5D-5L-proxy (EQ-5D-5L), and Mini-Mental State Examination (MMSE), respectively.

Caregiving costs for residents were basically covered by the national caregiving insurance system, which was separated from the national health insurance system in 2000. Claims data for caregiving insurance system were stored in each institute. Monthly caregiving costs were derived from claims data of Life Company Limited in March 2019 and March 2020. The annual caregiving costs were estimated using monthly data in March 2019.

Questionnaire

Barthel Index

BI is an index used to assess ADL. BI was first used in 1955 and was published in 1965. Using BI,

ADL was measured on a scale of 0 to 100, with higher scores indicating more independence from physical assistance [24].

EuroQoL-5D-5L-proxy

The EQ-5D-5L questionnaire was used to evaluate health-related QoL and was developed by the task force of the EuroQoL Group. Using EQ-5D-5L, health-related QoL was assessed on a scale of a negative value to 1, with 0 indicating death and 1 indicating a healthy status [25, 26]. Japanese tariff was developed in 2015. [27]. A fewer number of questions would be preferred, as the survey would be conducted during caregivers' routine work. In a previous study, which was conducted in Japan, EQ-5D-5L was used to measure the QoL in relation to AD [15]. It is possible that QoL in relation to AD could be detected through EQ-5D-5L, and therefore, EQ-5D-5L was used in this study.

Mini-Mental State Examination

MMSE was used to measure cognitive ability. It was also used to assess the severity of dementia. The maximum score that could be achieved in MMSE is 30 [28]. MMSE has been introduced in the guidelines for the diagnosis of dementia in Japan [29]. Accordingly, patients with MMSE scores of 21–23, 11–20, and 0–10 were classified as having mild, moderate, and severe AD, respectively. Patients with scores of 24–27 were suspected of having mild cognitive impairment (MCI) [30, 31].

Data analysis

Overall, patients with MMSE scores of 24–30 were considered to have a mild disease because medicines for AD were prescribed for them, and score volatility was a possibility (Supplementary Figure 1). After classifying the patients based on their MMSE score, BI scores, EQ-5D-5L scores, and annual caregiving costs in March 2019 were assessed using the Jonckheere-Terpstra test [32–34]. A multiple regression analysis was performed after all variables were standardized using two combinations of variables. In the first combination, the EQ-5D-5L scores were considered the objective variable, and age, sex, BI scores, and MMSE scores were the explanatory variables. In the other combination, the annual caregiving cost was the objective variable, whereas age, sex, support/care level needed, BI scores, and MMSE scores were considered explanatory variables. Average differences in the EQ-5D-5L scores, BI scores, and annual caregiv-

ing costs between March 2019 and March 2020 were evaluated according to the classifications in March 2019 and March 2020 for residents who did not leave the facilities during this period. Statistical significance was set at a p -value of <0.05 and all analyses were performed using Python version 3.7.7.

Ethics

This study was approved by the ethics committee of the Graduate School of Pharmaceutical Science, Faculty of Pharmaceutical Science, The University of Tokyo and informed consent was obtained from all participants when they decided to shift to facilities for the elderly run by Life Company Limited. If individuals were not capable of providing consent, as in the case of patients with severe AD, informed consent was obtained by a proxy from their family.

RESULTS

According to the patients' prescriptions, 401 out of the 3,461 patients enrolled were prescribed medicines for AD in March 2019, and 287 (71.2%) of these completed the entire questionnaire. Two hundred seventy-five (71.1%) of the 401 records of caregiving activities were obtained in March 2019. The mean age of the patients in the mild, moderate, and severe groups and the corresponding proportions of women in these groups are shown in Table 1. The number of people according to disease severities in March 2019 and March 2020 is shown in Table 2. The changes in certification for support or care level are shown in Fig. 1.

BI

The Jonckheere-Terpstra test showed that as AD severity worsened, the BI scores significantly decreased. The mean BI scores for the mild, moderate, and severe groups are shown in Table 3. The average difference in the BI scores between March 2019 and March 2020 ($n = 112$) are shown in Table 4.

EQ-5D-5L

The Jonckheere-Terpstra test revealed that as AD severity worsened, the EQ-5D-5L scores significantly decreased. The mean EQ-5D-5L scores for the mild, moderate, and severe groups are shown in Table 3. Based on the results of the multiple regression analysis, formula (1) was obtained (Table 5). The BI

Table 1
Characteristic of patients according to the severity of AD

	All	Mild	Moderate	Severe
Number of people	287	53	118	116
Sex (Women %)	76.7%	71.7%	76.3%	79.3%
Age (y) (mean ± SD)	86.1 ± 6.4	84.0 ± 6.9	86.6 ± 5.9	86.6 ± 6.5
Care level (level > 3, %)	47.4%	28.3%	32.2%	71.6%
Concomitant drugs (%)				
Antidiabetic	17.1%	15.1%	16.9%	18.1%
Antihypertensive	67.9%	64.2%	75.4%	62.1%
Antithrombotic	27.5%	26.4%	27.1%	28.4%
Laxative	60.3%	47.2%	64.4%	62.1%
Psychotropic	47.4%	47.2%	47.5%	47%

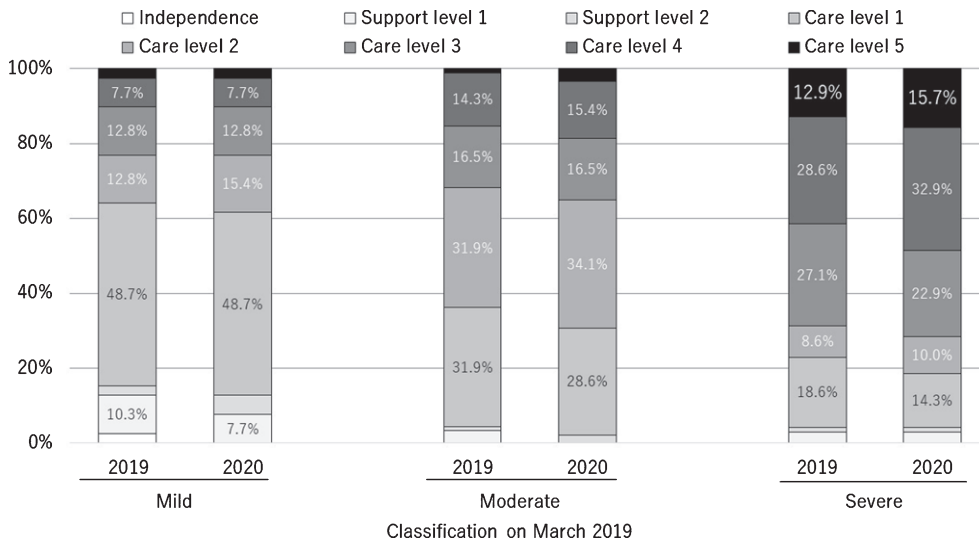


Fig. 1. Certifications for long-term care or support need in March 2019 and 2020 according to the severity of dementia in March 2019.

Table 2
Distribution of patients according to AD severity in March 2019 and 2020

Classification in March 2019	Classification in March 2020			All
	Mild	Moderate	Severe	
Mild	11	9	3	23
Moderate	7	31	11	49
Severe	0	3	47	50

score was a significant variable, whereas sex, age, and MMSE scores were not. The average differences in the EQ-5D-5L score between March 2019 and March 2020 ($n = 119$) for the three groups are shown in Table 4.

$$EQ\ 5D\ 5L = 0.00564 \times Sex - 0.0442 \times Age + 0.880 \times BI - 0.00533 \times MMSE + 4.163 \times 10^{-17} \quad (1)$$

Caregiving costs

The Jonckheere-Terpstra test showed that as the severity of AD worsened, annual caregiving costs significantly increased. The mean annual caregiving costs for the three groups are listed in Table 3. Based on the results of the multiple regression analysis, formula (2) was obtained (Table 5). Support/care level and MMSE scores were significant variables, whereas sex, age, and BI scores were not. The average differences in the annual caregiving costs between March 2019 and March 2020 ($n = 95$) for the three groups are shown in Table 4.

Caregiving costs =

$$0.0672 \times Sex + 0.0735 \times Age - 0.102 \times BI - 0.207 \times MMSE + 0.279 \times Care\ level\ 01 + 0.302 \times Care\ level\ 02 - 1.388 \times 10^{-17} \quad (2)$$

Table 3
Summary of the results in March 2019

	All	Mild	Moderate	Severe	Jonckheere-Terpstra test	
					z statistics	p
BI score (mean ± SD)	55.4 ± 33.8	83.6 ± 20.2	65.1 ± 26.9	32.8 ± 30.7	10.25	p < 0.001
Number of patients	287	53	118	116		
EQ-5D-5L score (mean ± SD)	0.596 ± 0.265	0.801 ± 0.223	0.662 ± 0.229	0.436 ± 0.222	9.22	p < 0.001
Number of patients	287	53	118	116		
Caregiving costs (million JPY, mean)	2.540 ± 0.724	2.111 ± 0.906	2.470 ± 0.637	2.809 ± 0.591	6.52	p < 0.001
Number of patients	275	52	111	112		

Table 4
Average differences in EQ-5D-5L scores, BI score, and caregiving costs between March 2019 and March 2020

	All	Classification in March 2020		
		Mild	Moderate	Severe
BI score (mean)				
Mild	-9.8	-2.3	-11.1	-33.3
Number of patients	23	11	9	3**
Moderate	-7.5	2.9	-7.0	-15.5
Number of patients	46	7	28	11
Severe	-9.7	NA*	8.3	-11.0
Number of patients	43	0	3**	40
EQ-5D-5L score (mean)				
Mild	-0.0778	-0.00415	-0.151	-0.126
Number of patients	23	11	9	3**
Moderate	0.00468	0.0561	0.0415	-0.132
Number of patients	49	7	31	11
Severe	-0.0152	NA*	0.124	-0.0247
Number of patients	47	0	3**	44
Annual caregiving costs (JPY, mean)				
Mild	-3,356	79,794	-41,027	-102,210
Number of patients	16	6	8	2**
Moderate	187,770	262,718	40,092	533,135
Number of patients	37	6	23	8
Severe	112,031	NA*	40,748	117,514
Number of patients	42	0	3**	39

*Not available because no one was transferred from the severe group to the mild group. **Only few (less than 5) patients were observed.

DISCUSSION

The objective of our study to evaluate the effects of severity of AD on ADL, QoL, and caregiving costs in Japanese facilities for the elderly. We found that as AD severity increased, ADL and QoL significantly decreased, and caregiving costs significantly increased. Moreover, it is possible that AD progression impaired ADL and QoL and increased caregiving costs with some exceptions.

The findings of our study are consistent with those reported previously, that is, ADL and QoL decrease according to the severity of AD [17–20]. However, the multiple regression analysis revealed that the MMSE score, which is the benchmark of AD severity, did not significantly affect the EQ-5D-5L score.

It is known that the BI score strongly correlates with the EQ-5D-5L score [35, 36]. Moreover, the MMSE score correlates with the BI score. The effects of MMSE score on the EQ-5D-5L score are relatively lower than those of the BI score. Therefore, the MMSE scores were not significant (Table 5). Regardless of the severity of AD at the start of the study, ADL and QoL decreased as AD progressed (Table 4).

To our knowledge, this is the first study to show that caregiving costs in facilities for the elderly in Japan increase according to the severity of AD. The caregiving insurance systems in Japan are mainly of two types: in-home based service and institution-based service. The types of service are not defined via locations where services are provided but via location where patients' daily lives are based on.

Table 5
Results of the multiple regression analysis in March 2019

Independent variable	Dependent variable	Coefficient	p
EQ-5D-5L	Sex*	0.00564	0.844
	Age	-0.0442	0.125
	BI	0.880	<0.001
	MMSE	-0.00533	0.883
	Constant	4.163×10^{-17}	1.000
Caregiving costs	Sex	0.0672	0.190
	Age	0.0735	0.154
	BI	-0.102	0.157
	MMSE	-0.207	0.00130
	Care-level-01***	0.279	<0.001
	Care-level-02***	0.302	<0.001
	Constant	-1.388×10^{-17}	1.000

*Female: 1, Male: 0. **Dummy variables. Care need level.01, Care need level.02)=(1, 0) indicates independence, support level 1 or 2, (Care need level.01, Care need level.02)=(0, 1) indicates care level 1 or 2, and (Care need level.01, Care need level.02)=(1, 1) indicates care level 3, 4, or 5.

Subsequently, some institutionalized individuals might be categorized to “in-home” services, as long as a regulatory agency regarded that their daily lives would be better in their homes.

Participants enrolled in our cohort were “institutionalized”; however, their services were provided via “in-home” service. The annual “in-home” care service per patient with dementia is reportedly 1.572 million JPY [12], which is lower than 2.540 million JPY in the present study. This is because Sado et al. included the type of service provided to patients in their homes.

The mean annual caregiving costs of nursing homes or residential facilities with health and caregiving services for the elderly were estimated to be 2.388 million JPY using the statistics from the Ministry of Health, Labour and Welfare [37]. Caregiving costs reported in this study are consistent with this value. Further studies on the relationship between the caregiving costs of various types of care services and AD progression are warranted.

The result of the statistical test, that is, caregiving costs increase according to the severity of AD, is consistent with the result of the multiple regression analysis, in which caregiving cost was the objective variable. As the MMSE score decreases, indicating worsening of AD, the caregiving costs increase (Table 5). The caregiving costs of the moderate and severe groups in March 2019 increased as AD progressed. However, that of the mild group did not increase. This is partially because the number of

patients in each group classified by AD severity in March 2019 and 2020 was not sufficient to detect the effect of disease progression on the caregiving costs. The extent of increase in the caregiving costs for the moderate group was higher than that for the remaining two groups. This is partially due to the existence of the “ceiling” or the upper limit of monthly caregiving costs covered by the public caregiving insurance system. The ceiling value varies depending on one’s caregiving level. The difference in value was higher between levels 2 and 3 (73,000 JPY) than between levels 3 and 4 (39,000 JPY) and between levels 4 and 5 (52,000 JPY) [13]. Given that more people were already receiving care of level 3 or higher initially in the severe group, the annual difference in caregiving costs might be higher for the moderate group. The range of change was likely to be smaller in the severe group, which already had a higher proportion.

Our study focused only on patients who were prescribed medicines for AD. This is because we excluded the other causes of cognitive impairment, such as schizophrenia and depression [29]. We found that some patients were prescribed AD medications while they showed MCI or were normal based on their MMSE scores. This finding is attributable to various reasons, such as the volatility of the MMSE score (i.e., MMSE scores might occasionally be higher for “true” AD patients) or false-positive results, whereby patients without AD might be misdiagnosed with AD and receive anti-AD medications (Supplementary Table 1).

There were four main limitations to our study. First, patients with AD were defined based on the prescription of anti-AD medications. Therefore, patients with AD not taking medications would be excluded. On the contrary, patients with dementias other than AD, such as vascular dementia or dementia with Lewy bodies, prescribed with anti-AD medications would be included as patients with AD. While not so many patients would be misclassified into AD patients, generalizability issues should be considered when the results extrapolated to a broader setting. Second, this study was conducted in facilities for the elderly in Japan. It has been reported that the QoL of patients with AD differs from that of patients who receive care services [38]. The care service cost also differs based on the type of service [13]. Therefore, the results of this study should be interpreted carefully before considering their application in all patients with AD. Third, there could be confounding factors other than the severity of AD. According to the prescription data in March 2019, there was no significant difference in

comorbidities among the three groups. Furthermore, there was no significant difference in the health statuses between March 2019 and March 2020 (Table 1, Supplementary Table 2). However, it is impossible to assert that there are no factors other than those derived from prescriptions that could significantly affect the study results. Finally, some residents who participated in this study in March 2019 moved out of the residential facilities by March 2020. This could have affected the study results.

In conclusion, as AD worsens, outcomes such as ADL and QoL worsen and caregiving costs increase. This study is unique in that it is the first study in Japan to evaluate the impact of the severity of AD on outcomes and caregiving costs over time, in addition to conducting a cross-sectional evaluation. Despite the limitations, the findings of this study are significant. Further research is warranted to provide epidemiological or economic evidence for the impact of dementia, which could facilitate a discussion on the allocation of scarce healthcare resources in a super-aged society in the near future.

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SUPPLEMENTARY MATERIAL

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