number of studies have shown relationships between nutritional impairment and morbidity, functional decline, and mortality in older people.[6–8] Nonetheless, few studies have examined the relationships between nutritional status and geriatric conditions among older people in various settings.

To answer these questions, in the present study we examined whether or not nutritional status might be associated with the accumulation of geriatric conditions or which conditions might be associated with poor nutritional status among dependent older people living in the community and in nursing homes.

Methods

Participants

The present study consisted of baseline data of the participants in two different prospective cohort studies. One was a multidisciplinary intervention care program trial of community-dwelling older adults (age 65years or older) who were eligible for Japanese long-term care insurance program, lived in Nagoya City, Japan, and were receiving various home care services from the Nagoya City Health Care Service Foundation for Older People, which has 16 visiting nursing stations associated with care-management centers (control $n = 511$, intervention $n = 601$, total participants $n = 1112$). The participants enrolled between 1 June 2009 and 30 November 2009 were scheduled to undergo comprehensive in-home assessments by trained nurses to constitute baseline data. Among those participants, participants allocated to an intervention group were enrolled in the present study, as the nutritional evaluation was carried out only in the intervention group at baseline. The second group was an observational prospective cohort based on the residents of 12 nursing homes ($n = 657$) located in Nagoya City, Japan. The participants were enrolled between 1 May 2009 and 30 June 2009.

In community-dwelling and nursing home cohorts, 90 and 70 participants were excluded, respectively, because of the lack of nutritional evaluation data. Thus, baseline data on 511 (male $n = 216$, female $n = 295$, mean age 81.2 ± 7.9 years [SD]) community-dwelling participants and 587 (male $n = 108$, female $n = 479$, mean age 85.1 ± 7.8 years [SD]) nursing home participants were used for the analysis.

Written informed consent for participation was obtained from all participants or, for those with substantial cognitive impairment, from a surrogate (usually the closest relative or legal guardian) according to the procedures approved by the institutional review board of Nagoya University Graduate School of Medicine.

Data collection

The data were collected by trained nurses at the participants' homes or nursing homes from standardized interviews with patients or surrogates and caregivers, and from the records of care-management centers or nursing homes. The data included participants' demographic characteristics and the Barthel Index, a rating for 10 basic activities of daily living (bADL; bathing, bladder function, bowel function, dressing, feeding, grooming, mobility, stairs, toilet use and transfers) using summary scores ranging from 0 (total disability) to 100 (no disability). Information on the number of drugs that participants were taking, and the following physician-diagnosed chronic conditions were also obtained from care-management center records and from nursing home medical records: ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes, dementia, cancer, hypertension and other diseases comprising the Charlson Comorbidity Index,[9] which represents a sum of weighted indexes taking into account the number and seriousness of pre-existing comorbid conditions (range 0–19, with a higher value indicating higher comorbidity). To obtain the greatest possible uniformity of data collection in different settings, the nurses were trained in the interviewing of participants and in the collection of data with standardized questionnaires.

Evaluation of nutritional status

In the present study, nutritional status was assessed at baseline by the Mini Nutritional Assessment short form (MNA-SF), one of the most valid and most frequently used nutritional screening tools for older persons.[10,11] MNA-SF consists of six items: food intake, weight loss, mobility, psychological stress or acute disease, neuropsychological problems and body mass index (BMI). The maximum score of MNA-SF is 14. A score equal to or less than 7 points is regarded as an indicator of malnutrition, 8–11 points indicate a risk for malnutrition and equal to or more than 12–14 points indicate that the person is well nourished.[12] We previously validated MNA and MNA-SF in Japanese older people.[13]

Definition of geriatric conditions

We defined geriatric conditions as collections of symptoms common in older adults, not necessarily associated with a specific disease, that increase in prevalence with age.[14,15] In the present study, we used the following eight symptoms as geriatric conditions: (i) vision impairment (poor eyesight or blindness despite use of corrective lenses); (ii) hearing impairment (poor hearing despite use of hearing aids); (iii) falls (at least one fall in the past 12 months); (iv) bladder control problems including not only urinary incontinence, but also catheterization, and an inability to control urination alone; (v) cognitive impairment (dementia diagnosed by a physician or the presence of apparent cognitive impairment); (vi) impaired mobility (requiring person assistance to walk or an inability to walk); (vii) swallowing disturbance (presence of abnormal volitional cough, abnormal gag reflex, dysphonia, dysarthria, cough after swallowing and voice change after swallowing); and (viii) loss of appetite (self-reported loss or reduced intake not attributable to specific reasons). The presence of geriatric conditions was self-reported by the participants in the standardized interview carried out by the nurses; or, for those with substantial cognitive impairment, it was reported by a surrogate, caregiver or trained nurses. The accumulation of geriatric conditions was defined by the number of symptoms that a patient had among eight symptoms as described. For the analysis, we also used six of the eight symptoms; that is, we excluded "swallowing disturbance" and "loss of appetite", which are closely related to nutritional status. Low BMI or low bodyweight was frequently included in geriatric conditions. These two conditions were not used in the present study, as they are directly involved in nutritional status.

Statistical analysis

Continuous variables were described by the use of statistical characteristics (means, SD). Discrete variables were described as counts and percentages. Analysis of variance or the χ^2-test was used to determine the differences among the MNA-SF classifications. Pearson's linear correlation coefficient and partial rank correlation coefficients adjusted for age and sex were used to measure the relationships between the MNA-SF score and the accumulated number of geriatric conditions. A *P*-value of <0.05 was taken to define statistical significance. We used univariate and multivariable logistic regression to determine which variables, including the presence of geriatric conditions, predicted malnourished versus well-nourished status evaluated with MNA-SF. For the multivariable logistic regression analysis, two models were used. Model I included sex, age, living settings (community or nursing home), the number of geriatric conditions among eight or six symptoms, and chronic diseases, such as diabetes mellitus and hypertension, which were significantly associated with malnutrition in univariate analysis. Model II included sex, age, living settings (community or nursing home) and all of the geriatric conditions. SPSS 15.0 (SPSS, Chicago, IL, USA) statistical software was used to analyze the data.

Results

The baseline characteristics of a total of 1098 participants aged 65years or over were compared among MNA-SF categories (Table 1). According to the MNA-SF classification, 21.4% (*n* = 235), 54.3% (*n* = 596) and 24.3% (*n* = 267) were categorized as "malnourished", "at risk of malnutrition" and "well nourished", respectively. The distribution of classifications differed significantly between institutionalized and community-dwelling participants. Compared with community-dwelling participants, the institutionalized older people had a higher prevalence of malnutrition and a lower rate of good nutrition when compared among the three groups of participants with different nutritional status classified by MNA scores. Significant differences were also detected in age, sex, prevalence of artificial nutrition, and scores of bADL and Charlson comorbidity index. Regarding the prevalences of chronic diseases, only those of diabetes mellitus and hypertension were found to be different among the three groups. There was also a significant difference in the number of geriatric conditions among MNA-SF classifications (Table 2). Poorer nutritional status according to the MNA-SF classification increased the number of geriatric conditions. Accumulation was higher in the malnourished group than in the "at risk of malnourishment" (among eight symptoms, among six symptoms) and in the "well-nourished" group (among eight, among six). There were significant differences among classes with regard to the prevalence of all the individual components of geriatric conditions. A higher prevalence of all of the components except falls was found in the poorer nutritional status.

As shown in Table 3, a significant negative correlation was detected between the number of accumulated geriatric conditions and the MNA-SF score. These correlations persisted after adjusting for age and sex. Similar results were observed when the accumulation of geriatric conditions was based on a total of six rather than eight symptoms. These results showed that participants suffering poorer nutritional status were more likely to have geriatric conditions.

Logistic regression analyses were carried out to evaluate the associations of variables including geriatric conditions with malnourished status evaluated with MNA-SF (Table 4). Unadjusted univariate analysis suggested that women, older age, lower bADL score, nursing home residence, the use of artificial nutrition, the number of drugs which participants were taking, the number of accumulated geriatric conditions (among eight symptoms OR 2.62, 95% CI 2.22–3.10; among six OR 2.36, 95% CI 2.00–2.78) and the presence of all of the components of geriatric conditions were associated with malnourishment. However, no association was observed with the Charlson Comorbidity Index or with the presence of chronic diseases, except diabetes mellitus and hypertension. Participants with either of these two lifestyle-related diseases were less likely to be malnourished.

Table 1 Nursing homes and community: baseline characteristics of participants by Mini Nutritional Assessment

	MNA (0–7) Malnourished	MNA (8–11) At risk of malnutrition	MNA (12–14) Well nourished	*P*-value
Nursing homes, *n* (% of total)	151 (25.7)	337 (57.4)	99 (16.8)	
Community, *n* (% of total)	84 (16.2)	259 (50.5)	168 (33.3)	<0.001
Nursing homes and community, *n* (% of total)	235 (21.4)	596 (54.3)	267 (24.3)	
MNA-SF score, mean (SD): nursing home*	6.1 (1.2)	9.2 (1.11)	12.5 (0.68)	<0.001
MNA-SF score, mean (SD): community*	5.8 (1.5)	9.6 (1.1)	12.5 (0.7)	<0.001
MNA-SF score, mean (SD): nursing home and community*	6.0 (1.3)	9.4 (1.1)	12.5 (0.7)	<0.001
Age, mean (SD)*	84.6 years (8.2)	83.8 years (8.1)	81.0 years (7.5)	<0.001
Men, *n* (% of men/total)	60 (25.5)	163 (27.3)	101 (37.8)	0.002
Artificial nutrition (% of total)	30 (12.8)	30 (5.0)	2 (0.7)	<0.001
Mean basic ADL, range 0–100 (SD)*	25.3 (27.0)	46.5 (30.9)	71.2 (23.9)	<0.001
No. drugs, mean (SD)*	5.0 (3.1)	5.6 (3.4)	7.2 (3.9)	<0.001
Charlson Comorbidity Index, mean (SD)*	2.6 (1.8)	2.4 (1.6)	2.6 (1.8)	0.045
Chronic diseases, *n* (% of total)				
Ischemic heart disease	36 (15.3)	99 (16.6)	47 (17.6)	0.790
Congestive heart failure	44 (18.7)	97 (16.3)	51 (19.1)	0.512
COPD	28 (12.0)	55 (9.2)	33 (12.4)	0.283
Cerebrovascular disease	104 (44.4)	270 (45.5)	118 (44.2)	0.929
Diabetes mellitus	32 (13.6)	88 (14.8)	76 (28.5)	<0.001
Cancer	13 (5.5)	33 (5.5)	16 (6.0)	0.961
Hypertension	102 (43.4)	294 (49.3)	169 (63.3)	<0.001

*Analysis of variance; others were analyzed using the χ^2-test. ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; MNA, Mini Nutritional Assessment.

Table 2 Nursing homes and community: baseline characteristics of participants by Mini Nutritional Assessment

	MNA (0–7) Malnourished	MNA (8–11) At risk of malnutrition	MNA (12–14) Well nourished	*P*-value
Nursing homes, *n* (% of total)	151 (25.7)	337 (57.4)	99 (16.8)	
Community, *n* (% of total)	84 (16.2)	259 (50.5)	168 (33.3)	<0.001
Nursing homes and community, *n* (% of total)	235 (21.4)	596 (54.3)	267 (24.3)	
No. geriatric conditions, mean (SD)†				
Among 8	4.7 (1.6)	3.5 (1.6)	2.3 (1.5)	<0.001
Among 6	3.6 (1.3)	2.9 (1.4)	2.1 (1.3)	<0.001
Geriatric conditions, *n* (% of total)				
Vision impairment	115 (49.8)	220 (37.5)	71 (26.7)	<0.001
Hearing impairment	123 (53.0)	250 (42.4)	89 (33.5)	<0.001
Falls	36 (15.4)	118 (19.9)	78 (29.2)	<0.001
Bladder control problem	205 (87.6)	415 (70.3)	105 (39.3)	<0.001
Cognitive impairment	161 (69.1)	326 (55.3)	96 (36.4)	<0.001
Mobility impairment	210 (89.7)	413 (69.4)	115 (43.1)	<0.001
Swallowing problem	138 (59.5)	213 (35.9)	52 (19.5)	<0.001
Appetite loss	123 (56.2)	148 (25.2)	21 (7.9)	<0.001

†Analysis of variance; others were analyzed using the χ^2-test. The geriatric conditions among eight included vision impairment, hearing impairment, falls, bladder control problem, cognitive impairment, mobility impairment, swallowing problem and appetite loss; among six included vision impairment, hearing impairment, falls, bladder control problem, cognitive impairment, and mobility impairment.

Table 3 Association of the accumulation of the geriatric conditions in participants from nursing homes and community with MNA-SF score

	No. geriatric conditions Among 8†		No. geriatric conditions Among 6‡	
	r	*P*	*r*	*P*
MNA-SF				
Unadjusted	−0.495	<0.001	−0.392	<0.001
Adjusted§	−0.473	<0.001	−0.364	<0.001

†The geriatric conditions among eight included vision impairment, hearing impairment, falls, bladder control problem, cognitive impairment, mobility impairment, swallowing problem and appetite loss; ‡among six included vision impairment, hearing impairment, falls, bladder control problem, cognitive impairment, and mobility impairment. §Adjusted by age and sex. MNA, Mini Nutritional Assessment.

In multivariate analysis, the number of accumulated geriatric conditions was associated with malnourishment (in model I OR 2.51, 95% CI 2.11–3.00). When the number of accumulated geriatric conditions was based on a total of six rather than eight, similar results were observed (in model I, OR 2.21, 95% CI 1.86–2.64). In model I, diabetes mellitus and hypertension were no longer associated with malnourishment. It should be noted that, in model I, the significant association between the number of accumulated geriatric conditions and malnourishment persisted when the bADL score was included in the analysis (among eight OR 1.74, 95% CI 1.40–2.10; among six OR 1.26, 95% CI 1.01–1.57). Although nursing home residents were associated with malnourishment, there was no longer an association when the bADL score was included in the analysis (OR 1.32, 95% CI 074–2.35). In model II, which used each geriatric condition component instead of the number of accumulated conditions, the presence of a bladder control problem, cognitive impairment, mobility impairment, swallowing problem and appetite loss were each associated with malnourishment. In model II, sex, age and nursing home residence were not associated with malnourishment.

Discussion

The present study showed that nursing home residents had a higher prevalence of malnutrition (25.7%) than those living in the community (16.2%). Furthermore, both 16.8% and 33.3% of the institutionalized and community-dwelling older people, respectively, were well nourished. A study of elderly Germans estimated that 36.7% and 85.7% of institutionalized and community-dwelling participants, respectively, were well nourished, based on MNA-SF for nutritional evaluation.[16] In a study of elderly Taiwanese, 26.5% and 80.1% of institutionalized and community-dwelling participants, respectively, were considered well nourished according to MNA-SF categories.[17] The lower prevalence of well-nourished community-dwelling older people in the present study seems attributable to the multiple medical problems and the functional limitations among our participants.

Those with poorer nutritional status were older, had lower bADL scores and were more likely to use artificial alimentation. Although we do not know the exact reasons for the relationships between artificial nutrition and poor nutritional status, it is possible that those patients receive insufficient nutrients or that those receiving artificial nutrition have a background of a heavy disease burden.

It has been reported that functional disability in older people is associated with inadequate diet and weight loss.[18,19] Huang *et al.* compared the nutritional status of their functionally dependent and independent elderly patients, and found poor nutritional status with lower daily caloric intake in the former group.[20] Consistently in the present study, participants with lower classified MNA-SF were associated with a lower bADL score. We observed that presence of diabetes mellitus or hypertension is negatively associated with malnutrition, although these associations disappeared after adjustment. The participants with these chronic diseases had higher BMI levels than those without disease (diabetes mellitus 21.8 ± 3.6 *vs* 20.1 ± 3.7, $P < 0.001$; hypertension 21.1 ± 3.9 *vs* 19.6 ± 3.5, $P < 0.001$), consistent with MNA-SF evaluation, suggesting the participants with diabetes mellitus or hypertension seem to have better nutritional status compared with those without these chronic diseases.

We clearly showed that, among dependent older people in nursing homes and in the community, those with poorer nutritional status had more geriatric conditions. In fact, an increase of one geriatric condition among eight or six symptoms showed 2.62 or 2.36 OR of the risk of malnutrition in univariate analyses. It should be emphasized that the association persisted

Table 4 Nursing homes and community: factors associated with malnutrition

	Univariate			Multivariate model I			Multivariate model II		
	OR	(95% CI)	*P*	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Women (*vs* men)	1.78	1.22–2.62	0.003	0.93	0.54–1.61	0.796	0.80	0.43–1.50	0.491
Age (continuous)	1.06	1.04–1.09	<0.001	1.00	0.97–1.03	0.946	1.03	0.99–1.06	0.194
Basic ADL (continuous)	0.95	0.94–0.96	<0.001						
Nursing home (*vs* community)	3.17	2.20–4.57	<0.001	2.25	1.34–3.77	0.002	1.31	0.68–2.52	0.413
Artificial nutrition (% of total)	19.30	4.56–81.68	<0.001						
No. drugs	0.84	0.79–0.88	<0.001	0.90	0.84–0.97	0.006	0.90	0.83–0.98	0.016
No. geriatric conditions									
Among 8	2.62	2.22–3.10	<0.001	2.51	2.11–3.00	<0.001			
Among 6	2.36	2.00–2.78	<0.001	2.21	1.86–2.64	<0.001			
Vision impairment	2.72	1.87–1.87	<0.001				1.57	0.87–2.85	0.137
Hearing impairment	2.22	1.55–3.19	<0.001				0.93	0.51–1.70	0.805
Falls experiences	0.45	0.29–0.70	<0.001				0.58	0.29–1.15	0.119
Bladder control problem	10.96	6.92–17.36	<0.001				3.27	1.72–6.21	<0.001
Cognitive impairment	3.94	2.71–5.72	<0.001				2.50	1.40–4.45	0.002
Mobility impairment	11.62	7.14–18.91	<0.001				4.73	2.39–9.37	<0.001
Swallowing problem	6.01	4.03–8.96	<0.001				2.59	1.43–4.69	0.002
Appetite loss	15.07	8.97–25.33	<0.001				16.45	7.84–34.54	<0.001
Chronic diseases, presence (*vs* absence)									
Charlson Comorbidity Index	0.99	0.90–1.09	0.844						
Ischemic heart disease	0.84	0.52–1.35	0.479						
Congestive heart failure	1.00	0.64–1.56	0.992						
COPD	0.96	0.56–1.64	0.879						
Cerebrovascular disease	1.00	0.70–1.43	0.989						
Diabetes mellitus	0.39	0.25–0.62	<0.001	0.62	0.34–1.13	0.118			
Cancer	0.91	0.43–1.94	0.816						
Hypertension	0.45	0.31–0.64	<0.001	0.92	0.55–1.56	0.766			

The geriatric conditions among eight included vision impairment, hearing impairment, falls, bladder control problem, cognitive impairment, mobility impairment, swallowing problem and appetite loss; among six included vision impairment, hearing impairment, falls, bladder control problem, cognitive impairment, and mobility impairment. ADL, activities of daily living; COPD, chronic obstructive pulmonary disease.

even after controlling for sex, age, bADL, living settings and comorbidities. Recently in a cross-sectional hospital-based observational study, Saka *et al.* also reported that patients who were malnourished or at risk of malnourishment according to the MNA full version had more geriatric conditions.[21] Although they reported that those with low MNA scores had more chronic diseases, in the present study comorbidity was not positively associated with malnutrition. This inconsistency seems to be related to the different settings of the surveys. Saka *et al.* investigated hospital-based older patients, but our participants lived in the community or in nursing homes and did not have active diseases. Thus, nutritional status is closely related to the accumulation of geriatric conditions, but not to comorbidities, at least in dependent elderly people without acute illness.

We also observed that malnutrition was associated with various components of geriatric conditions. In the crude model, the presence of each component, except for falls, was more likely to be classified as malnutrition. In contrast, participants who had fallen were less likely to be malnourished. We observed that the bADL score of those who experienced falls was lower than that of those who did not experience falls (63.6 ± 24.4 *vs* 47.3 ± 34.3, $P < 0.001$). This relationship between falls and malnutrition appeared through bADL status, as this association disappeared after adjusting for bADL status (OR 0.82, 95% CI 0.47–1.41). Participants with the poorest bADL status (severe physical limitation, such as typically confined to bed) are less likely to fall.[22] The poorest bADL status is associated with poorer nutritional status, as described earlier.

After demographic adjustments, the presence of a bladder control problem, cognitive impairment, mobility impairment, a swallowing problem and appetite loss were each significantly associated with malnutrition. The exact reasons for the association between bladder control problems and malnutrition remain unknown. It is well documented that being overweight is a risk factor for urinary incontinence.[23] However, in the present study of dependent older people, we found the opposite result. One reason for this discrepancy might be the definition of bladder control problems, which in the present study included not only urinary incontinence, but also catheterization and an inability to control urination. There are many risk factors common to the development of both a bladder control problem and malnutrition. These common factors include bADL status, depression and multiple medical conditions.[24,25] It is also true for mobility impairment, which is also associated with malnutrition.

Many of the studies investigating the relationships between cognition and nutritional status focus on nutritional deficiencies as a consequence of dementia or cognitive decline. For instance, cognitive decline might impair the ability or desire to eat.[26] Weight loss and changed eating behavior are recognized characteristics of the progressive dementing process, and uncontrolled weight loss is almost inevitable in the latter stages.[27]

We showed the associations between malnutrition according to the MNA-SF classification, and both the presence of a swallowing problem and appetite loss. The impairment of swallowing function can have devastating health implications. These include not only aspiration pneumonia, but also malnutrition and dehydration, as well as changes in health status, including an increased need for care provision, especially for older adults. In fact, a recent large cross-sectional survey of geriatric wards of hospitals showed that swallowing difficulties were strongly associated with malnutrition.[28,29] How appetite control changes with age remains to be elucidated, but a loss of appetite is frequently observed with aging; in a phenomenon called the "anorexia of aging", the physiological reductions in appetite and food intake accompany normal aging or occur as a consequence of various diseases. Appetite loss and subsequent reduced oral intake are followed of course by weight loss and nutritional impairment.[30] However, it should be noted that despite the exclusion of these conditions that are directly linked to reduced energy intake, the accumulation of geriatric conditions (six items) is associated with poor nutritional status in dependent elderly.

In the present study, 42.3% and 18.4% of the participants in the community and nursing homes were male, respectively. One of the reasons for this difference of the ratio of males and females might be due to the different average age of the participants. The participants from nursing homes were much older than those from the community. The male gender ratio tends to reduce as age increases, and among the elderly there is usually an excess of females.

The present study had several strengths, including the relatively large number of participants in different settings: nursing homes and the community. Our analyses took into account potential confounders including age, sex, bADL status and comorbidity.

The present study had potential limitations, however. Data obtained from multiple nurses through standardized interviews might be inaccurate, although to minimize discordance in data collection, nurses were trained in interviewing older participants and caregivers before the start of the study. The degree of cognitive impairment was not included in the analysis, as cognitive function was not evaluated by a specific screening instrument. There is no consensus on the definition of a geriatric condition or what conditions that category should include. In the present study, potential key conditions/diseases, such as dizziness, delirium or pressure sores, osteoporosis, gastroesophageal reflux disease, chronic kidney disease and dyslipidemia, were not included in the analysis. Although mood, such as depression, might influence nutritional status, depressive status was not evaluated in the present study. The study used cross-sectional analysis, and we cannot draw conclusions about cause and effect. Further research is required to examine geriatric conditions and their longitudinal associations with nutritional status.

Acknowledgements

We thank all participants and staff who took part in this study. This study was financially supported by Grant-in-Aid for the Comprehensive Research on Aging and Health from the Ministry of Health, Labor, and Welfare of Japan.

Disclosure statement

The authors declare no conflict of interest.

References

1 The National Institute of Population and Social Security Research has issued a report on future demographic trends in Japan: cabinet office government of Japan. 1994 [Cited 2007 Jul 13.] Available from URL: Available from: http://www5.cao.go.jp/keizai3/keizaiwp/wp-je96/wp-je96fu-3-4-2fc-a.html
2 Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the Health and Retirement Study. *Ann Intern Med* 2007; **147**: 156–164.
3 Ahmed T, Haboubi N. Assessment and management of nutrition in older people and its importance to health. *Clin Interv Aging* 2010; **5**: 207–216.
4 Guigoz Y. The Mini Nutritional Assessment (MNA) review of the literature – what does it tell us? *Nutr Health Aging* 2006; **10**: 466–485; discussion 485–487.
5 Sloane PD, Ivey J, Helton M, Barrick AL, Cerna A. Nutritional issues in long-term care. *J Am Med Dir Assoc* 2008; **9**: 476–485.
6 Brown JS, Vittinghoff E, Lin F, Nyberg LM, Kusek JW, Kanaya AM. Prevalence and risk factors for urinary incontinence in women with type 2 diabetes and impaired fasting glucose: findings from the National Health and Nutrition Examination Survey (NHANES) 2001–2002. *Diabetes Care* 2006; **29**: 1307–1312.
7 Rich MW. Heart failure in older adults. *Med Clin North Am* 2006; **90**: 863–885.
8 Schwartz AV, Hillier TA, Sellmeyer DE *et al.* Older women with diabetes have a higher risk of falls: a prospective study. *Diabetes Care* 2002; **25**: 1749–1754.
9 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–383.
10 Bauer JM, Kaiser MJ, Anthony P, Guigoz Y, Sieber CC. The Mini Nutritional Assessment-its history, today's practice, and future perspectives. *Nutr Clin Pract* 2008; **23**: 388–396.
11 Vellas B, Villars H, Abellan G *et al.* Overview of the MNAFIts history and challenges. *J Nutr Health Aging* 2006; **10**: 456–463.
12 DiMaria-Ghalili RA, Guenter PA. The mini nutritional assessment. *Am J Nurs* 2008; **108**: 50–59.
13 Kuzuya M, Kanda S, Koike T, Suzuki Y, Satake S, Iguchi A. Evaluation of Mini-Nutritional Assessment for Japanese frail elderly. *Nutrition* 2005; **21**: 498–503.
14 Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the Health and Retirement Study. *Ann Intern Med* 2007; **147**: 156–164.
15 Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *JAMA* 1995; **273**: 1348–1353.
16 Kaiser MJ, Bauer JM, Uter W *et al.* Prospective validation of the modified mini nutritional assessment short-forms in the community, nursing home, and rehabilitation setting. *J Am Geriatr Soc* 2011; **59**: 2124–2128.
17 Tsai AC, Chang TL, Wang YC, Liao CY. Population-specific short-form mini nutritional assessment with body mass index or calf circumference can predict risk of malnutrition in community-living or institutionalized elderly people in Taiwan. *J Am Diet Assoc* 2010; **110**: 1328–1334.
18 Morley JE. Anorexia of aging: physiologic and pathologic. *Am J Clin Nutr* 1997; **66**: 760–773.
19 Payette H, Gray-Donald K, Cyr R, Boutier V. Predictors of dietary intake in a functionally dependent elderly population in the community. *Am J Public Health* 1995; **85**: 677–683.
20 Huang YC, Wueng SL, Ou CC, Cheng CH, Su KH. Nutritional status of functionally dependent and nonfunctionally dependent elderly in Taiwan. *J Am Coll Nutr* 2001; **20** (Suppl 2): 135–142.
21 Saka B, Kaya O, Ozturk GB, Erten N, Karan MA. Malnutrition in the elderly and its relationship with other geriatric syndromes. *Clin Nutr* 2010; **29**: 745–748.
22 Kron M, Loy S, Sturm E, Nikolaus T, Becker C. Risk indicators for falls in institutionalized frail elderly. *Am J Epidemiol* 2003; **158**: 645–653.
23 Subak LL, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. *J Urol* 2009; **182** (Suppl 6): S2–S7.
24 Gurina NA, Frolova EV, Degryse JM. A roadmap of aging in Russia: the prevalence of frailty in community-dwelling older adults in the St. Petersburg district – the "Crystal" study. *J Am Geriatr Soc* 2011; **59**: 980–988.
25 Araki A, Ito H. Diabetes mellitus and geriatric syndromes. *Geriatr Gerontol Int* 2009; **9**: 105–114.
26 Incalzi RA, Capparella O, Gemma A *et al.* Inadequate caloric intake: a risk factor for mortality of geriatric patients in the acute-care hospital. *Age Ageing* 1998; **27**: 303–310.
27 Claggett MS. Nutritional factors relevant to Alzheimer's disease. *J Am Diet Assoc* 1989; **89**: 392–396.
28 Vanderwee K, Clays E, Bocquaert I, Gobert M, Folens B, Defloor T. Malnutrition and associated factors in elderly hospital patients: a Belgian cross-sectional, multi-centre study. *Clin Nutr* 2010; **29**: 469–476.
29 White GN, O'Rourke F, Ong BS, Cordato DJ, Chan DK. Dysphagia: causes, assessment, treatment, and management. *Geriatrics* 2008; **63**: 15–20.
30 Wernette CM, White BD, Zizza CA. Signaling proteins that influence energy intake may affect unintentional weight loss in elderly persons. *J Am Diet Assoc* 2011; **111**: 864–873.

Geriatrics Gerontology Medline Indexed

Geriatr Gerontol Int 2014; **14:** *819–826*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Relationship between small cerebral white matter lesions and cognitive function in patients with Alzheimer's disease and amnestic mild cognitive impairment

Taeko Makino, Hiroyuki Umegaki, Yusuke Suzuki, Madoka Yanagawa, Zen Nonogaki, Hirotaka Nakashima and Masafumi Kuzuya

Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

Aim: The main purpose of the present study was to investigate the influence of small cerebral white matter lesions on cognitive functions, and its difference by clinical stage.

Methods: A total of 160 patients with Alzheimer's disease and 40 older adults with amnestic mild cognitive impairment were enrolled in the present study. The Fazekas rating scale was used for the semi-quantitative measurement of white matter lesions. Participants whose scales were more than grade 2 were excluded. Associations between the degree of small white matter lesions and cognitive functions including memory, verbal fluency, working memory, processing speed, and executive function were examined.

Results: We found that small white matter lesions influenced the performances of neuropsychological tests differently between Alzheimer's disease and amnestic mild cognitive impairment. Analysis of covariance showed significant effects of interaction on a test that assessed categorical verbal fluency. In the amnestic mild cognitive impairment group, small periventricular white matter hyperintensities were significantly associated with poor performances in categorical verbal fluency; whereas in the Alzheimer's disease group, such associations were not observed. Deep white matter hyperintensities did not influence any cognitive functions examined in both groups.

Conclusions: The results suggested the involvement of periventricular small white matter lesions on impairment in verbal fluency, and such influence might be different depending on an individual's clinical stage. **Geriatr Gerontol Int 2014; 14: 819–826.**

Keywords: Alzheimer's disease, cognitive function, mild cognitive impairment, verbal fluency, white matter lesions.

Introduction

Cerebral white matter lesions (WML) are identified as white matter hyperintensities, areas with high signal intensities on T2-weighed magnetic resonance imaging (MRI). The pathogenesis of WML has not been fully clarified, and the clinical relevance of WML also remains ambiguous. Several histopathological correlates have been reported: enlarged WML including myelin pallor, tissue rarefaction associated with loss of myelin and axons, and mild gliosis.[1,2] The occurrence of WML has been shown to increase with advancing age,[3,4] and the progression of WML has been associated with vascular risk factors.[5] In a meta-analysis, WML predicted an increased risk of stroke, dementia and death.[6]

In some non-demented population-based studies, WML predicted a higher rate of cognitive decline,[4,7–10] especially when located in the periventricular regions.[11–14] In some studies of Alzheimer's disease (AD) patients, it has been suggested that AD patients with WML had worse cognitive performances than those without WML,[15–17] whereas other studies did not find any association between WML and cognitive decline in AD patients.[18,19] Diversities in study samples with varying clinical stages or different methods for the assessment of WML might explain the inconsistent results in those studies. Several studies have suggested that WML could influence cognitive performance in the

Accepted for publication 8 September 2013.

Correspondence: Dr Hiroyuki Umegaki MD PhD, Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya-shi 466-8550, Japan. Email: umegaki@med.nagoya-u.ac.jp

doi: 10.1111/ggi.12176

early stages of AD, but not in the late stages.[18,20] If this is true, WML might have greater influence on cognitive profiles in amnestic mild cognitive impairment (aMCI) patients than AD patients, because aMCI has been considered a preclinical and prodromal stage of AD. In some studies of MCI patients, WML were associated with cognitive decline,[21] and predicted a higher rate of conversion to dementia.[22,23] Studies investigating the influence of WML on cognitive function both in AD and aMCI patients have been sparse to date.

In view of investigating the influence of small WML on cognitive profiles of AD pathology, one has to preclude with caution a possible contamination of mixed pathology, such as vascular dementia or vascular mild cognitive impairment, from analysis. Therefore, in the present study, we focused on investigating neuropsychological traits in patients with AD or aMCI, and examined their associations with the degree of small WML, assessed by a semi-quantitative method based on MRI findings after carefully excluding patients with diffuse or extensive WML. If any difference was observed between the groups, the finding might suggest temporal profiles regarding the influence of small WML on cognitive performances during the progression of this neurocognitive disorder.

Methods

Participants

The present study was carried out among outpatients attending the Nagoya University Hospital department of geriatrics in Nagoya, Japan, between January 2010 and March 2012. Among 641 consecutive patients aged 60 years or older, 268 patients who were diagnosed with neither AD nor aMCI, and 109 patients who could not complete the relevant cognitive tasks were excluded. Regarding methods for objectively assessing the degree of WML, the Fazekas rating scale[24] was used in the present study. It is a visual semi-quantitative rating scale of WML volume, and this scale is one of the most widely-used and well-validated. This scoring system is a four-point scale, rated on a 0- to 3-point scale of increasing severity. As explained in the Introduction, in order to eliminate a possible contamination of mixed pathology, those who were graded more than 2 on the Fazekas rating scale (64 patients) were not included in the study, and only those who were graded either 0 or 1 on the scale were included, eventually leaving 200 patients subjected for analyses.

Of the participants, 160 patients were diagnosed as probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[25] and 40 cases were diagnosed as aMCI according to the Mayo Clinic Criteria.[26] The patients with aMCI all met the criteria for single-domain amnestic MCI or multiple-domain amnestic MCI proposed by Petersen.[27] All of them had the complaint of memory impairment. Patients with single-domain amnestic MCI had impaired performance (more than 1.5 SD below controls) on one or more of the memory tests used in the neuropsychological battery, but not on the other tests. Patients with multiple-domain amnestic MCI had impaired performance on one or more of the memory tests, and impaired performance on one or more of the other tests. None of them had dementia according to the clinical assessment. Hereafter, aMCI includes both the single- and multiple-domain subtypes.

The evaluation procedure consisted of a detailed medical history, cognitive assessment, laboratory tests and cerebral MRI. The patients also underwent a clinical examination to exclude other etiologies. Patients who had a history of cerebrovascular disorders or the presence of significant vascular risk factors were excluded, as well as patients who had previously received an actual diagnosis of major depression.[28] Japanese was the primary language for all participants.

Cognitive assessment

All participants underwent a battery of neuropsychological tests. The battery of neuropsychological tests included the following tests: the Mini-Mental State Examination (MMSE)[29] for general cognitive function; the Logical Memory I and II subtests of the Wechsler Memory Scale-revised (WMS-R)[30] for memory; the category fluency test (participants were required to generate as many animal names as possible within 1 min) and the letter fluency test (participants were required to generate as many words beginning with the syllable "ka" (the Japanese version of the phonemic fluency task) as possible within 1 min for verbal fluency; the Digit Span Forward and Backward subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R)[31] for working memory; the Digit Symbol subtests of WAIS-R[31] for processing speed; and the Stroop colored word test for executive functions (controlled inhibition). All patients were also assessed for depressive mood using the Geriatric Depression Scale-15 (GDS-15).[32]

Testing and scoring of the neuropsychological tests were carried out by a trained clinical psychologist with a Master's degree in clinical psychology. Participants were tested individually in a single session. Written informed consent was obtained at the start of the evaluation from all participants or their closest relative.

White matter assessment

The MRI scans were carried out on a 1.5T machine. Ratings of WML on MRI images were carried out on a

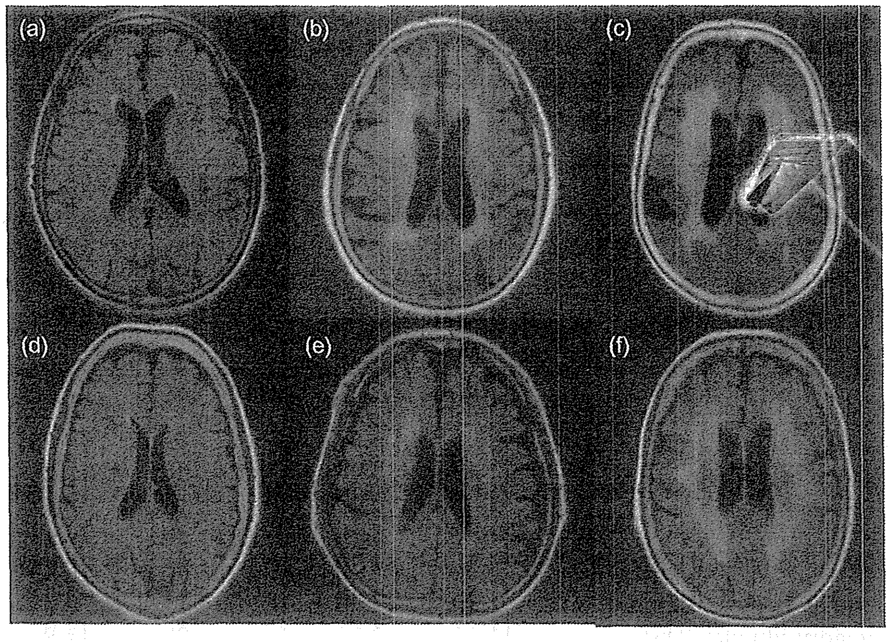

Figure 1 Examples of Fazekas scale ratings. (a) Periventricular hyperintensities (PVH) score = 1. (b) PVH score = 2. (c) PVH score = 3. (d) Deep white matter hyperintensities (DWMH) score = 1. (e) DWMH score = 2. (f) DWMH score = 3.

Table 1 Numbers of patients for Fazekas scale ratings

		AD (n = 160) DWMH Grade 0	AD (n = 160) DWMH Grade 1			aMCI (n = 40) DWMH Grade 0	aMCI (n = 40) DWMH Grade 1
PVH	Grade 0	30	14	PVH	Grade 0	5	4
	Grade 1	21	95		Grade 1	7	24

Definitions of rating scores of periventricular white matter hyperintensity (PVH): grade 0, absence; grade 1, caps or pencil-thin lining. Definitions of rating scores of deep subcortical white matter hyperintensity (DWMH): grade 0, absence; grade 1, punctate.
AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment.

computer screen with axial fluid-attenuated inversion recovery (FLAIR) images. The visual semi-quantitative rating scale of WML volume described by Fazekas *et al.*[24] was used. This scoring system is a four-point scale for separately assessing the increasing severity of periventricular white matter hyperintensity (PVH) and deep subcortical white matter hyperintensity (DWMH). PVH severity was scored according to the following categories: absence (grade 0); caps or pencil-thin lining (grade 1); smooth halo (grade 2) and irregular PVH extending into the deep white matter (grade 3). DWMH severity was scored according to the following categories: absence (grade 0); punctate (grade 1); beginning confluence (grade 2) and large confluence (grade 3). Examples of PVH and DWMH severities are shown in Figure 1. Participants who were graded more than grade 2 of PVH or DWMH were excluded from the present study. Table 1 shows the numbers of patients for the Fazekas rating scale included in this study. All ratings were carried out by two raters (the second and third authors). Each rater rated each case individually and then consulted with each other to reach a consensus.

Statistical analysis

The statistical analyses were carried out using IBM SPSS Statistics version 19 for Windows (SPSS Japan, Tokyo, Japan). A value of $P < 0.05$ was used in all analyses to show statistical significance.

First, we carried out descriptive analyses of sociodemographic and clinical characteristics. Table 2 shows the mean and standard deviations, and the frequency and percentage. We used the χ^2-test for the comparison of categorical data, and we applied Student's t-test for continuous data.

Analysis of covariance (ANCOVA) was used to determine the correlation of WML and cognitive data between AD and aMCI. It is well known that age and

Table 2 Clinical characteristics and cognitive performance of Alzheimer's disease and amnestic mild cognitive impairment patients

	AD (n = 160)				aMCI (n = 40)				
Sex (male/female)	66/94				15/25				
Diabetes mellitus (%)	29 (18.13%)				7 (17.50%)				
Hypertension (%)	70 (43.75%)				20 (50.00%)				
Hyperlipidemia (%)	70 (43.75%)				20 (50.00%)				
aMCI subtype (single domain/multiple domain)					19/21				
	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	P-value
Age (years)	77.01	6.87	61	92	76.08	6.56	60	90	0.440
Education (years)	11.40	2.78	6	20	12.26	2.95	8	18	0.084
GDS15	4.33	3.37	0	14	3.83	2.94	0	13	0.390
MMSE	21.94	3.69	11	29	27.13	1.49	24	30	<0.001
WMS-R Logical Memory I	6.26	4.30	0	22	10.05	4.65	1	22	<0.001
WMS-R Logical Memory I	1.16	2.40	0	12	3.20	2.83	0	9	<0.001
Category Fluency Test	11.67	3.72	2	23	14.90	4.02	6	24	<0.001
Letter Fluency Test	7.76	3.15	2	20	9.18	3.40	0	15	0.013
WAIS-R Digit-Span Forward	5.63	1.89	2	10	6.20	1.68	3	9	0.084
WAIS-R Digit-Span Backward	4.34	1.45	1	8	5.05	1.38	2	8	0.006
WAIS-R Digit-Symbol	33.22	11.73	3	77	38.38	12.01	9	68	0.014
Stroop Test Color	21.86	10.03	9.56	78.09	17.67	3.94	8.85	30.79	<0.001
Stroop Test Colored Word	46.75	20.04	15.40	134.19	40.08	18.03	20.32	113.21	0.056

P-values were calculated by Student's t-tests. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; Education, total number of years of schooling; GDS15, 15-item version of the Geriatric Depression Scale; MAX, maximum score; MIN, minimum score; MMSE, Mini-Mental State Examination; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

education level influence cognitive function, so these two variables were considered to be covariables in the analysis carried out later. As a post-hoc analysis, pairwise multiple comparisons of the cognitive data were tested with Bonferroni test after ANCOVA.

Results

Table 2 presents the sociodemographic and clinical characteristics of the participants, and the raw neuropsychological test results for both AD and aMCI. The means and standard deviations, and maximal and minimal values are shown.

The groups with different diagnoses were not statistically different in terms of the following variables: distribution of sex, clinical comorbidity (diabetes mellitus, hypertension, hyperlipidemia), age, years of education and depressive mood (GDS-15). Likewise, the MCI subtypes were similar in their distributions of the variables. Regarding the comparison of cognitive performances between the two groups, AD group performed significantly worse than did the aMCI group in tests as follows: MMSE (t [158.87] = 13.84, $P < 0.001$), logical memory I (t [198] = 4.91, $P < 0.001$), logical memory II (t [198] = 4.63, $P < 0.001$), category fluency (t [198] = 4.83, $P < 0.001$), letter fluency (t [198] = 2.51, $P < 0.05$), digit span backward (t [198] = 2.80, $P < 0.01$), digit symbol (t [198] = 2.47, $P < 0.05$) and Stroop color test (t [162.81] = 2.59, $P < 0.001$).

Table 3 shows the influence diagnosis and PVH had on participants' performances in the neuropsychological tests, as well as the interaction between the two factors. We found that diagnosis significantly influenced the results of the following tests: MMSE (F [1,194] = 49.43, $P < 0.001$), logical memory I (F [1,194] = 16.81, $P < 0.001$), logical memory II (F [1,194] = 14.68, $P < 0.001$), category fluency (F [1,194] = 29.43, $P < 0.001$), letter fluency (F [1,194] = 8.02, $P < 0.01$), digit symbol (F [1,194] = 4.86, $P < 0.05$) and Stroop colored word test (F [1,194] = 4.06, $P < 0.05$). PVH had a significant influence on the results of the tests that assess the following variables: category fluency (F [1,194] = 8.11, $P < 0.01$) and letter fluency (F [1,194] = 5.47, $P < 0.05$). Individuals having small PVH, independent of their diagnosis, performed worse than those having no PVH in terms of verbal fluency. We found significant effects of interaction on the results of the category fluency test (F [1,194] = 7.01, $P < 0.01$). The

Table 3 Cognitive performance according to periventricular hyperintensities

	AD				aMCI				P	P	P
	PVH grade0 (n = 44)		PVH grade1 (n = 116)		PVH grade0 (n = 9)		PVH grade1 (n = 31)		Diagnosis	PVH	Diagnosis × PVH
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
MMSE	22.82	3.04	21.60	3.86	27.67	1.22	26.97	1.54	<0.001	0.294	0.678
WMS-R Logical Memory-I	6.77	4.19	6.06	4.35	11.22	5.45	9.71	4.43	<0.001	0.500	0.651
WMS-R Logical Memory-II	1.09	2.61	1.19	2.32	3.44	3.32	3.13	2.73	<0.001	0.819	0.676
Category Fluency Test	12.25	3.11	11.45	3.92	18.44	3.68	13.87	3.55	<0.001	0.005	0.009
Letter Fluency Test	8.34	2.96	7.53	3.20	11.44	1.33	8.52	3.54	0.005	0.020	0.094
WAIS-R Digit-Span Forward	6.11	1.98	5.45	1.83	6.22	1.79	6.19	1.68	0.473	0.723	0.402
WAIS-R Digit-Span Backward	4.86	1.29	4.14	1.47	5.33	1.80	4.97	1.25	0.074	0.165	0.503
WAIS-R Digit-Symbol	36.11	12.24	32.12	11.40	44.78	11.97	36.52	11.55	0.029	0.105	0.304
Stroop Test Color	20.54	8.28	22.36	10.61	16.46	3.13	18.01	4.13	0.051	0.701	0.991
Stroop Test Colored Word	44.37	16.03	47.66	21.36	30.75	7.09	42.78	19.38	0.045	0.163	0.259

P-values were calculated by analysis of covariance and adjusted for age and education. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; PVH, periventricular white matter hyperintensity; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

combination of aMCI and category fluency showed a significant negative influence (F [1,194] = 9.28, $P < 0.01$); whereas in the AD group, such an association was not observed.

Table 4 shows the influence that diagnosis and DWMH had on participants' performances on neuropsychological tests, as well as the interaction between the two factors. We found that diagnosis significantly influenced the results of the following tests: MMSE (F [1,194] = 56.00, $P < 0.001$), logical memory I (F [1,194] = 22.54, $P < 0.001$), logical memory II (F [1,194] = 21.09, $P < 0.001$), category fluency (F [1,194] = 16.06, $P < 0.001$), letter fluency (F [1,194] = 4.34, $P < 0.05$), digit span backward (F [1,194] = 4.02, $P < 0.05$). DWMH did not significantly influence any other neuropsychological tests. We did not find any other significant effects of the interaction between diagnosis and DWMH.

Discussion

The primary objective of the present study was to examine the association between small WML and cognitive function in older patients with AD or aMCI. To this end, two subgroups of patients with AD or aMCI differed regarding the influence of small WML on cognitive function.

Among aMCI participants, those without PVH had higher scores than those with PVH on the category fluency test. In contrast, the existence of small PVH did not significantly affect the score on the same test in AD patients. These findings might support a notion suggesting that WML could influence cognitive performance in the early stage of cognitive impairment, but not in the later stage of degenerative dementia.[18,20] Changes of relative involvement of WML on cognition by disease progression could explain the results obtained. It is well known that as AD pathology advances, cortical atrophy extends. Therefore, one could speculate that the relative influence of cortical atrophy on cognition compared with that of WML becomes increased in the later stage of AD. Further investigations focusing on patients with earlier stages of AD whose extent of cortical atrophy are considered minimal could address this speculation.

We found significant effects of interaction between diagnosis and PVH on the results of the category fluency test, whereas on the results of the letter fluency such interaction was not found. The category fluency task is associated with the ability to access semantic knowledge, whereas letter fluency is considered an index of frontal control function.[33] In a meta-analysis of verbal fluency in AD, it was suggested that impairment in category fluency rather than letter fluency might be among the early changes associated with AD.[34] A previous study has shown that the aMCI groups have

Table 4 Cognitive performance according to deep subcortical white matter hyperintensity

	AD				aMCI				P	P	P
	DWMH grade 0 (n = 51)		DWMH grade 1 (n = 109)		DWMH grade 0 (n = 12)		DWMH grade 1 (n = 28)		Diagnosis	DWMH	Diagnosis × DWMH
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
MMSE	22.53	3.48	21.66	3.76	27.00	1.48	27.18	1.52	<0.001	0.756	0.444
WMS-R Logical Memory-I	6.45	3.98	6.17	4.46	11.75	4.58	9.32	4.56	<0.001	0.213	0.161
WMS-R Logical Memory-II	1.16	2.41	1.17	2.40	4.17	2.98	2.79	2.71	<0.001	0.254	0.126
Category Fluency Test	11.96	3.65	11.53	3.76	14.67	4.96	15.00	3.65	<0.001	0.590	0.670
Letter Fluency Test	8.24	3.62	7.53	2.89	9.75	3.14	8.93	3.53	0.038	0.394	0.856
WAIS-R Digit-Span Forward	5.94	2.01	5.49	1.82	6.75	1.42	5.96	1.75	0.147	0.170	0.569
WAIS-R Digit-Span Backward	4.39	1.36	4.31	1.50	5.08	1.51	5.04	1.35	0.032	0.874	0.975
WAIS-R Digit-Symbol	36.96	12.60	31.47	10.93	40.33	12.22	37.54	12.04	0.112	0.221	0.621
Stroop Test Color	20.13	6.60	22.67	11.22	17.43	3.74	17.77	4.09	0.056	0.656	0.574
Stroop Test Colored Word	46.58	16.92	46.84	21.42	40.89	26.01	39.73	13.92	0.158	0.606	0.913

P-values were calculated by analysis of covariance and adjusted for age and education. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; DWMH, deep subcortical white matter hyperintensity; MMSE, Mini-Mental State Examination; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

greater impairment in category fluency performance than in letter fluency performance relative to healthy controls.[35] Neuroanatomically, category fluency relies on the medial temporal lobe regions, whereas letter fluency has been found to correlate with prefrontal lobe functioning.[36] Differences in the anatomical substrates for each verbal fluency task might explain the present results. Because of advanced medial temporal lobe atrophy, WML might not influence category fluency in the later stage of AD.

When diagnosis was not added, associations between the small PVH and low verbal fluency performance were shown in the present study. Several studies found that WML was particularly associated with a decline in mental processing speed, executive functions, but not with a decline in memory functions,[10,37–39] which could suggest that WML have an influence on frontal lobe functions. Memory decline is particularly related to medial temporal lobe atrophy, and might be less affected by WML.[17,40] The disruption of long associating fibers by PVH might be particularly deleterious for frontal lobe domain functions.[21] In the present results, small PVH contributed to cognitive decline in verbal fluency, but not in any other domains of cognitive function. It remains unclear why small PVH was correlated only with verbal fluency.

Our results are in line with several population-based studies[11–14] in which PVH and not are associated with different clinical conditions. It is also suggested that the pathology presenting PVH might impair cognitive functioning more easily than that affecting the subcortical area. Anatomically, the periventricular regions have a high density of long associating fibers, which connect the cortex with the subcortical nuclei and other distant brain territories, whereas the subcortical area has a high density of short-looped U fibers connecting adjacent gyri.[11] The mechanism underlying the present results requires further substantiation.

The main limitation of the present study was the rating system of WML. Regarding the semi-quantitative rating of white matter lesions used in our study, it could be argued that it is not sufficiently accurate, but this rating system has been shown to correlate well with quantitative volumetric measurements.[41] The present study showed that small amounts of WML were correlated with cognitive impairment. We assumed that greater degrees of WML correspond to different patterns of cognitive decline. WML could trigger or enhance neurodegenerative processes when the lesion load reaches a certain threshold.[19]

Because of the smaller sample size of aMCI patients, the statistical power of the study might have been insufficient to detect an association between cognitive deficit and small WML. Our sample size was also inadequate to examine the association of cognitive decline with the different locations of DWMH, which might have some importance. Some studies have shown that cognitive dysfunction differs according to where WML are present.[42] It would therefore be important to assess the specific roles of WML depending on their frontal, parietal or temporal locations.

In summary, the present study found that small PVH were significantly associated with cognitive decline, in particular with a deficit of verbal fluency, in aMCI patients. Furthermore, a category fluency deficit, not a letter fluency deficit, was found to show an interaction with small PVH. Further studies are required to confirm these results and to improve our understanding of the underlying mechanisms.

Acknowledgments

We thank all the older adults who participated in the present study.

Disclosure statement

The authors declare no conflict of interest.

References

1 Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W. Histopathologic correlates of white-matter changes on MRI in Alzheimer's disease and normal aging. *Neurology* 1995; **45**: 883–888.
2 Fazekas F, Kleinert R, Offenbacher H *et al.* Pathological correlates of incidental MRI white-matter signal hyperintensities. *Neurology* 1993; **43**: 1683–1689.
3 de Leeuw FE, de Groot JC, Achten E *et al.* Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry* 2001; **70**: 9–14.
4 Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HBW. Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. *Lancet* 2000; **356**: 628–634.
5 Basile AM, Pantoni L, Pracucci G *et al.* Age, hypertension, and lacunar stroke are the major determinants of the severity of age-related white matter changes. *Cerebrovasc Dis* 2006; **21**: 315–322.
6 Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *Br Med J* 2010; **341**: c3666.
7 Schmidt R, Berghold A, Jokinen H *et al.* White matter lesion progression in LADIS frequency, clinical effects, and sample size calculations. *Stroke* 2012; **43**: 2643–2647.
8 Schmidt R, Ropele S, Enzinger C *et al.* White matter lesion progression, brain atrophy, and cognitive decline: the Austrian Stroke Prevention Study. *Ann Neurol* 2005; **58**: 610–616.
9 Garde E, Mortensen EL, Rostrup E, Paulson OB. Decline in intelligence is associated with progression in white matter hyperintensity volume. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1289–1291.
10 Prins ND, van Dijk EJ, den Heijer T *et al.* Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain* 2005; **128**: 2034–2041.
11 de Groot JC, de Leeuw FE, Oudkerk M *et al.* Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol* 2002; **52**: 335–341.
12 Prins ND, van Dijk EJ, den Heijer T *et al.* Cerebral white matter lesions and the risk of dementia. *Arch Neurol* 2004; **61**: 1531–1534.
13 van den Heuvel DMJ, ten Dam VH, de Craen AJM *et al.* Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. *J Neurol Neurosurg Psychiatry* 2006; **77**: 149–153.
14 Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk White matter hyperintensity progression matters. *Neurology* 2009; **73**: 120–125.
15 Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease – the nun study. *JAMA* 1997; **277**: 813–817.
16 Amar K, Bucks RS, Lewis T, Scott M, Wilcock GK. The effect of white matter low attenuation on cognitive performance in dementia of the Alzheimer type. *Age Ageing* 1996; **25**: 443–448.
17 Shim YS, Youn YC, Na DL *et al.* Effects of medial temporal atrophy and white matter hyperintensities on the cognitive functions in patients with Alzheimer's disease. *Eur Neurol* 2011; **66**: 75–82.
18 Jellinger KA. Small concomitant cerebrovascular lesions are not important for cognitive decline in severe Alzheimer disease. *Arch Neurol* 2001; **58**: 520–521.
19 Lee JH, Olichney JM, Hansen LA, Hofstetter CR, Thal LJ. Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer disease. *Arch Neurol* 2000; **57**: 1474–1479.
20 Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet* 1999; **354**: 919–920.
21 Debette S, Bombois S, Bruandet A *et al.* Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. *Stroke* 2007; **38**: 2924–2930.
22 Staekenborg SS, Koedam E, Hennernan WJP *et al.* Progression of mild cognitive impairment to dementia contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke* 2009; **40**: 1269–1274.
23 Bombois S, Debette S, Bruandet A *et al.* Vascular subcortical hyperintensities predict conversion to vascular and mixed dementia in MCI patients. *Stroke* 2008; **39**: 2046–2051.
24 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5-t in Alzheimer dementia and normal aging. *Am J Roentgenol* 1987; **149**: 351–356.
25 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**: 939–944.
26 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment – clinical characterization and outcome. *Arch Neurol* 1999; **56**: 303–308.
27 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004; **256**: 183–194.

28 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. Washington, DC: American Psychiatric Association, 1985.
29 Folstein MF, Folstein SE, McHugh PR. Mini-mental state – practical method for grading cognitive state of patients for clinician. *J Psychiatr Res* 1975; **12**: 189–198.
30 Wechsler D. *The Wechsler Memory Scale-Revised Manual*. San Antonio, TX: The Psychological Corporation, 1987.
31 Wechsler D. *The Wechsler Adult Intelligence Scale-Revised*. Toronto: The Psychological Corporation, 1981.
32 Sheikeh JI, Yesavage JA. Geriatric depression scale recent evidence and development of a short version. *Clin Gerontol* 1986; **5**: 165–173.
33 Nutter-Upham KE, Saykin AJ, Rabin LA *et al*. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Arch Clin Neuropsychol* 2008; **23**: 229–241.
34 Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia* 2004; **42**: 1212–1222.
35 Hanyu H, Kume KK, Takada Y, Onuma T, Iwamoto T. The 1-minute mental status examination in the memory clinic. *J Am Geriatr Soc* 2009; **57**: 1130–1131.
36 Rascovsky K, Salmon DP, Hansen LA, Thal LJ, Galasko D. Disparate letter and semantic category fluency deficits in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *Neuropsychology* 2007; **21**: 20–30.
37 Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Raininko R, Tilvis R. White-matter changes in healthy elderly persons correlate with attention and speed of mental processing. *Arch Neurol* 1993; **50**: 818–824.
38 de Groot JC, de Leeuw FE, Oudkerk M *et al*. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* 2000; **47**: 145–151.
39 Tullberg M, Fletcher E, DeCarli C *et al*. White matter lesions impair frontal lobe function regardless of their location. *Neurology* 2004; **63**: 246–253.
40 Mungas D, Jagust WJ, Reed BR *et al*. MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. *Neurology* 2001; **57**: 2229–2235.
41 van Straaten ECW, Fazekas F, Rostrup E *et al*. Impact of white matter hyperintensities scoring method on correlations with clinical data – the LADIS study. *Stroke* 2006; **37**: 836–840.
42 Ota M, Nemoto K, Sato N, Yamashita F, Asada T. Relationship between white matter changes and cognition in healthy elders. *Int J Geriatr Psychiatry* 2009; **24**: 1463–1469.

The Effect of Additional Training on Motor Outcomes at Discharge from Recovery Phase Rehabilitation Wards: A Survey from Multi-Center Stroke Data Bank in Japan

Nariaki Shiraishi[1,2]*, **Yusuke Suzuki**[3], **Daisuke Matsumoto**[4], **Seungwon Jeong**[5], **Motoya Sugiyama**[6], **Katsunori Kondo**[7], **Masafumi Kuzuya**[1]

1 Department of Geriatrics, Medicine in Growth and Aging, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan, **2** Department of Rehabilitation, Faculty of Health Science, Nihon Fukushi University, Nagoya, Japan, **3** Department of Comprehensive Community Care Systems, Nagoya University Graduate School of Medicine, Nagoya, Japan, **4** Department of Physical Therapy, Faculty of Health Science, Kio University, Koryo, Japan, **5** Department of Social Science Center for Gerontology and Social Science, Chubu Rosai Hospital, Nagoya, Japan, **6** Department of Rehabilitation, Chubu Rosai Hospital, Nagoya, Japan, **7** Center for Well-being and Society, Nihon Fukushi University, Nagoya, Japan

Abstract

Objectives: The purpose of the present study was to examine the potential benefits of additional training in patients admitted to recovery phase rehabilitation ward using the data bank of post-stroke patient registry.

Subjects and Methods: Subjects were 2507 inpatients admitted to recovery phase rehabilitation wards between November 2004 and November 2010. Participants were retrospectively divided into four groups based upon chart review; patients who received no additional rehabilitation, patients who were added with self-initiated off hours training, patients who were added with off hours training by ward staff, patients who received both self-initiated training and training by ward staff. Parameters for assessing outcomes included length of stay, motor/cognitive subscales of functional independent measures (FIM) and motor benefit of FIM calculated by subtracting the score at admission from that at discharge.

Results: Participants were stratified into three groups depending on the motor FIM at admission (≦28, 29~56, 57≦) for comparison. Regarding outcome variables, significant inter-group differences were observed in all items examined within the subgroup who scored 28 or less and between 29 and 56. Meanwhile no such trends were observed in the group who scored 57 or more compared with those who scored less. In a decision tree created based upon Exhaustive Chi-squared Automatic Interaction Detection method, variables chosen were the motor FIM at admission (the first node) additional training (the second node), the cognitive FIM at admission(the third node).

Conclusions: Overall the results suggest that additional training can compensate for the shortage of regular rehabilitation implemented in recovery phase rehabilitation ward, thus may contribute to improved outcomes assessed by motor FIM at discharge.

Citation: Shiraishi N, Suzuki Y, Matsumoto D, Jeong S, Sugiyama M, et al. (2014) The Effect of Additional Training on Motor Outcomes at Discharge from Recovery Phase Rehabilitation Wards: A Survey from Multi-Center Stroke Data Bank in Japan. PLoS ONE 9(3): e91738. doi:10.1371/journal.pone.0091738

Editor: Andreas Meisel, Charité Universitaetsmedizin Berlin, Germany

Received September 29, 2013; **Accepted** February 14, 2014; **Published** March 13, 2014

Funding: This study was supported by the Grant-in-Aid for Scientific Research (C) by The Ministry of Education, Culture, Sports, Science and Technology of the Japanese government, issued for the research project entitled "The effect of additional training after stroke: a data base study." The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: n-shira@n-fukushi.ac.jp

Introduction

Stroke is one of primary debilitating events that affect health status and functional capacity, and is reportedly ranked second or third cause of mortality or condition leading to functional impairments in most developed countries [1]. Japan is no exception that stroke is the first cause of conditions requiring care and is ranked the first in medical expenditure nationwide among the older population [2]. Recent advancement has made various therapeutic options including thrombolytic therapy, intravascular therapy or cerebral protective therapy available for stroke patients, however that does not undermine the significance of rehabilitation for functional recovery. It has been confirmed from previous randomized control trials (RCT) or systematic reviews that providing care in stroke units by multidisciplinary team comprising doctors, nurses, physiotherapist (PT), occupational therapist (OT) and speech therapist (ST) leads to improved clinical outcomes, such as long-term prognosis, activities of daily living at discharge, length of hospital stay [3,4]. To date, there had been a dearth of multi-center data base for rehabilitation medicine in Japan, which impeded implementation of studies supported by strong evidences. In order to establish rigorous evidences for the quality improvement and to provide rationales for the revision of reimbursement system in stroke rehabilitation, we have been establishing a data bank (DB) of post-stroke patients receiving rehabilitation since 2005, which was supported by a Grant-in-Aid issued from the

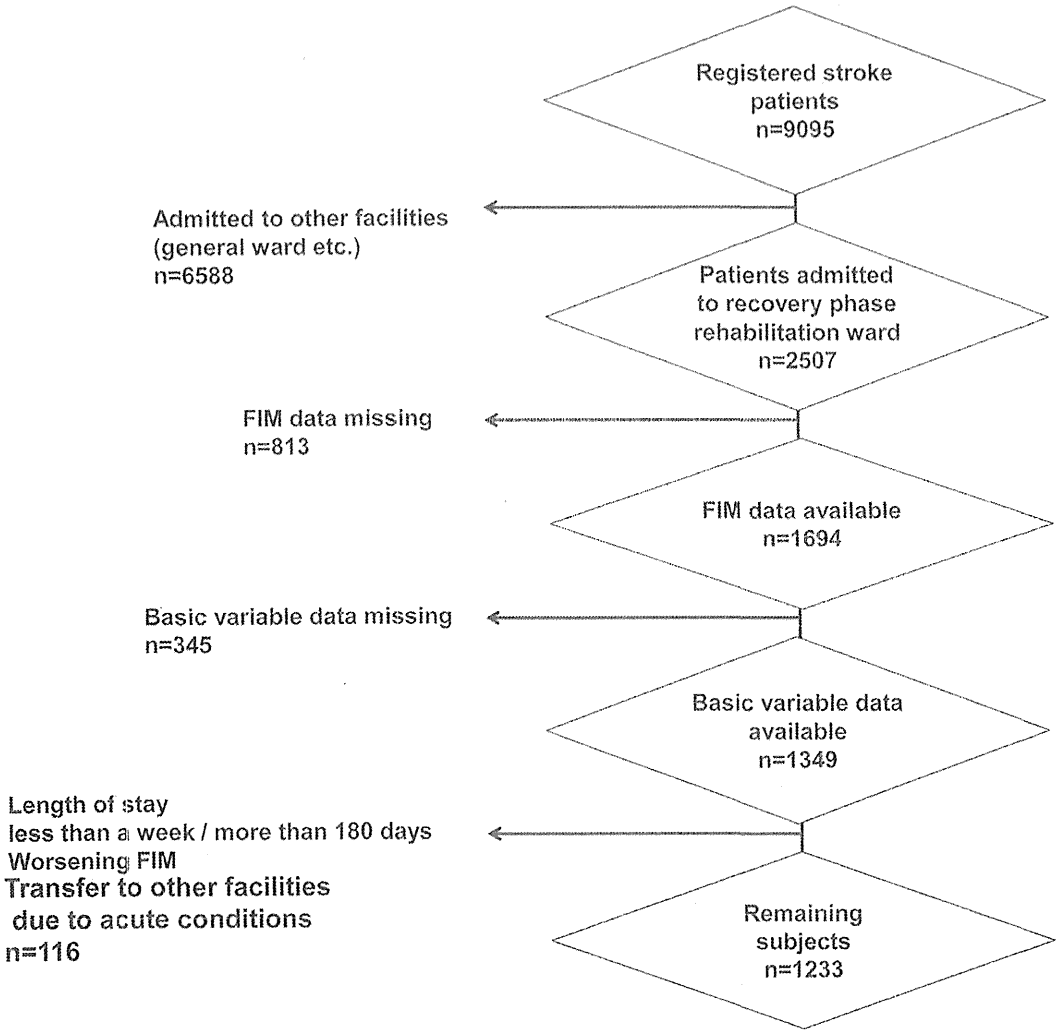

Figure 1. Flow chart showing selection procedure of participants.
doi:10.1371/journal.pone.0091738.g001

Ministry of Health, Labor and Welfare for the research project entitled "The development of data bank for stroke rehabilitation". By November 2011, we collected over 9000 cases from 30 institutions nationwide. In Japan recovery phase rehabilitation ward for patients took effect from the year 2000 and the 2006 revision for reimbursement enabled post stroke patients to receive a maximum of three hours rehabilitation per day by PT, OT and ST. This unique type of ward restricts intake of patient only to medical conditions such as stroke, spinal injuries, head trauma, hip fractures or disuse syndrome. In addition, there are specific regulations regarding the admission criteria, including term of admission. For example, stroke patients have to be admitted within two months after the onset of stroke with maximum length of stay limited until 150 days after the onset. Regarding the time of rehabilitation per day, only those who can tolerate three hours rehabilitation per day are eligible for the entry to rehabilitation programs according to the US Agency for Health Care Policy and Research [5], which is in contrast with the policy applied in Japan. On the other hand, there is a study implemented in a stroke unit that indicated the significance of "off hours" training enhanced by multidisciplinary team for improved activities of daily living (ADL) [1], which suggests a potential benefit of such off hours intervention particularly under the situation where there is a limitation in authorized volume of training. The "OFF hours" training comprises self-initiated training and training by ward staff. However, little attention to date has been paid to off hours intervention and its effect on functional prognosis [6,7]. As suggested in a recent meta-analysis, the importance of off hours training is a subject to be investigated through further research [8]. Although previous studies regarding off hours training focused on self-initiated training mainly led by patients themselves, there is also a necessity to evaluate additional training provided by ward staff. No studies so far had examined the effect of off hours training (self-initiated training, training by ward staff or both) in recovery phase rehabilitation wards uniquely introduced in Japan.

There is a difficulty in carrying out RCT in rehabilitation medicine. Therefore as an alternative method of investigation, well-designed comparative research with larger samples is considered significant [9]. However, there has been a concern about external validity in previous reports with such method since many of them either came from single institution or had not examined reproducibility in other samples of patients [9,10]. Thus in the present study, in order to endorse external validity, we obtained observational data from multiple sources and randomly assigned the individual data into two groups and examined

Table 1. Characteristics of participants stratified by motor subscales of FIM at admission.

Motor subscales of FIM at admission ≦28 (n = 427)

		①No additional training	②Self-initiated traning	③Training by ward staff	④Dual training	p value†	multiple
		(n = 62)	(n = 7)	(n = 203)	(n = 155)		comparison‡
Sex	Male	33(14.2%)	2(0.9%)	113(48.7%)	84(36.2%)	0.59	
	Female	29(14.9%)	5(2.6%)	90(46.2%)	71(36.4%)		
Type fo stroke	CI	38(14.7%)	3(1.2%)	132(51.2%)	85(32.9%)	0.02	
	CH	17(13.0)	2(1.5%)	50(38.2%)	62(47.3%)		
	SAH etc.	7(18.4%)	2(5.3%)	21(55.3%)	8(21.1%)		
Informal care resources	NIC	17(18.5%)	2(2.2%)	42(45.7%)	31(33.7%)	0.27	
	OIC	20(13.7%)	4(2.7%)	64(43.8%)	58(39.7%)		
	MTIC	19(10.6%)	1(0.6%)	94(52.5%)	65(36.3%)		
Age		74.5±9.9	73.0±8.0	75.3±9.2	69.4±11.8	<0.001	④<①③
Days after onset at admission		41.1±25.0	48.6±47.3	39.9±21.2	30.9±16.4	<0.001	④<①③

Motor subscales of FIM at admission 29~56 (n = 418)

		①No additional training	②Self-initiated traning	③Training by ward staff	④Dual training	p value†	multiple
		(n = 63)	(n = 16)	(n = 71)	(n = 268)		comparison‡
Sex	Male	50(18.9%)	13(4.9%)	43(16.2%)	159(60.0%)	0.01	
	Female	13(8.5%)	3(2.0%)	28(18.3%)	109(71.2%)		
Type of stroke	CI	27(10.2%)	11(4.1%)	58(21.8%)	170(63.9%)	<0.001	
	CH	31(13.9%)	2(0.9%)	11(8.9%)	79(64.2%)		
	SAH etc.	5(17.2%)	3(10.3%)	2(6.9%)	19(65.5%)		
Informal care resources	NIC	19(17.3%)	6(5.5%)	23(20.9%)	62(57.3%)	0.46	
	OIC	17(12.4%)	4(2.9%)	23(16.8%)	93(67.9%)		
	MTIC	26(15.7%)	6(3.6%)	23(13.9%)	111(66.9%)		
Age		71.8±9.5	68.1±9.7	75.1±10.7	66.6±12.8	<0.001	④<①③
Days after onset at admission		41.9±21.4	34.9±19.4	36.4±18.4	32.0±14.6	<0.001	④<①③

Motor subscales of FIM at admission 57≦ (n = 388)

		①No additional training	②Self-initiated traning	③Training by ward staff	④Dual training	p value†	multiple
		(n = 45)	(n = 41)	(n = 22)	(n = 280)		comparison‡
Sex	Male	23(9.3%)	31(12.6%)	13(5.3%)	180(72.9%)	0.12	
	Female	22(15.6%)	10(7.1%)	9(6.4%)	100(70.9%)		
Type of stroke	CI	28(11.2%)	16(6.4%)	16(6.4%)	190(76.0%)	0.003	

Table 1. Cont.

Motor subscales of FIM at admission ≤28 (n = 427)		①No additional training	②Self-initiated traning	③Training by ward staff	④Dual training	p value†	multiple comparison‡
		(n = 62)	(n = 7)	(n = 203)	(n = 155)		
	CH	9(9.8%)	17(18.5%)	2(2.2%)	64(69.6%)		
	SAH etc.	8(17.4%)	8(17.4%)	4(8.7%)	26(56.5)		
Informal care resources	NIC	12(12.0%)	13(13.0%)	0(0.0%)	75(75.0%)	0.07	
	OIC	15(11.7%)	13(10.2%)	9(7.0%)	91(71.1%)		
	MTIC	16(10.6%)	13(8.6%)	12(7.9%)	110(72.8%)		
Age		72.0±11.1	61.7±15.5	70.9±18.2	64.2±13.7	<0.001	②④<①
Days after onset at admission		35.4±16.8	34.6±14.4	41.6±26.8	30.4±21.9	0.05	

note:SAH = Subarachnoidal hemorrhage; CI = Cerebral infarction; CH = Cerebral hemorrhage; NIC = No informal caregivers; OIC = One informal caregiver; MTIC = More than two informal caregivers.
†p value for one way analysis of variance.
‡multiple comparison: digits refer to group numbers (Tukey multiple comparison procedure).
doi:10.1371/journal.pone.0091738.t001

whether the equation model formulated in one group can also predict the outcomes in the other with statistical significance.

The purpose of the present study was to examine potential benefit of off-hours rehabilitation involving self-initiated training by patients themselves, and training by ward staff in patients admitted to recovery phase rehabilitation wards using the DB of post-stroke patients registered during the term of observation.

Subjects and Methods

The present study was a secondary analysis of the DB of post-stroke patients registered between November 2004 and November 2010. Subjects were 2507 inpatients admitted to recovery phase rehabilitation wards out of 9095 patients registered in post-stroke DB. The DB was managed by the Japan Association of Rehabilitation Database (JARD) and the data was provided after the research protocol was approved by the institutional review board. Thus the data is not publicly available but only those who obtained the approval were authorized access to the DB. Of the subjects, those whose essential data (age, sex, FIM, record of self-initiated off hours training) were either absent or missing in more than 40% of inpatients, length of stay being either less than 7 days or more than 180 days, venue of rehabilitation changed due to acute medical conditions, FIM scores at discharge deteriorated were excluded, eventually 1233 inpatients were subjected to analyses (Fig. 1). Variables included age, sex and type of stroke as basic information. The followings were also included; number of days after admission, number of informal caregivers (none, single person, more than 2 people), total volume of PT and OT counted by Formal Therapy Unit (FTU) and FTU per day were also calculated (1FTU is equivalent to 20 minute Formal Therapy). Parameters for assessing outcomes included length of stay, motor FIM/cognitive FIM and motor benefit of FIM calculated by subtracting the score at admission from that at discharge. Participants were retrospectively divided into four groups based upon chart records; patients who received no additional rehabilitation (no additional training), patients who were added with self-initiated off hours training (self-initiated training), patients who were added with off hours training by ward staff (training by ward staff), patients who received both self-initiated off hours training and training by ward staff (dual additional training) and their outcomes assessed by parameters aforementioned were compared.

Statistical Analysis

Age, length of stay, number of days after the onset of stroke until discharge, FTU, FTU/day, motor FIM, cognitive FIM and motor benefit of FIM of the four intervention groups were compared using analysis of variance followed by Tukey's post-hoc test.It is known that improvement of ADLs during admission can be higher in patients whose physical independence at admission is intermediate compared with patients who have either low or high physical independence, thus exhibits reverse U-shaped trend [11]. Therefore, subjects were divided equally into three subgroups based on the motor FIM at admission for group comparison. Categorical data (sex, types of stroke and presence of informal caregivers) of the four groups were compared using chi-square test. In order to clarify contributing factors to motor FIM at discharge after possible confounding factors (presence of informal caregivers, motor FIM at admission and cognitive FIM at admission) having been adjusted, a decision tree analysis was carried out, making measured variables at admission that indicated significant inter-group differences by univariate analysis explanatory variables. In the present study Exhaustive Chi-Squared Automatic Interaction Detection (ECHAID) was adopted for the analysis. ECHAID is a

Table 2. Outcome parameters of participants at discharge stratified by motor subscales of FIM at admission.

	①No additional training (n = 62)	②Self-initiated traning (n = 7)	③Training by ward staff (n = 203)	④Dual training (n = 155)	p value†	multiple comparison‡
Motor subscales of FIM at admission ≤28 (n = 427)						
Length of stay	111.3±46.2	105.0±61.4	95.7±43.9	124.9±31.2	<0.001	①④>③
FTU*	358.8±184.0	308.7±252.9	275.3±179.2	474.4±221.4	<0.001	④>①>③
FTU/day*	3.2±1.0	3.2±1.8	2.8±1.2	3.8±1.4	<0.001	④>①③
Motor FIM at admission	17.9±5.0	16.9±3.9	16.3±4.2	20.2±4.9	<0.001	④>①③
Cognitive FIM at admission	11.4±6.4	15.0±8.6	11.9±6.4	17.9±8.3	<0.001	④>①③
Motor FIM at discharge	31.7±16.3	50.6±22.3	33.0±18.4	52.1±21.4	<0.001	④>①③
Cognitive FIM at discharge	15.0±7.7	21.7±8.5	15.9±6.4	24.6±8.3	<0.001	④>①③
Motor benefit of FIM	13.8±12.8	33.7±22.3	16.7±17.0	31.9±19.7	<0.001	④>①③, ②>①

	①No additional training (n = 63)	②Self-initiated traning (n = 16)	③Training by ward staff (n = 71)	④Dual training (n = 268)	p value†	multiple comparison‡
Motor subscales of FIM at admission 29~56 (n = 418)						
Length of stay	111.2±47.8	100.4±33.1	88.4±38.1	104.1±37.6	0.01	①④>③
FTU*	398.5±222.4	379.4±171.2	248.3±144.3	405.1±242.7	<0.01	①④>③
FTU/day*	3.5±1.0	3.8±0.8	2.8±1.1	3.7±1.5	<0.01	①②④>③
Motor FIM at admission	42.3±8.6	49.5±6.9	39.9±7.5	43.5±8.0	<0.01	②>①③④, ④>③
Cognitive FIM at admission	22.1±7.3	24.5±7.5	19.6±5.9	24.7±7.1	<0.01	④>①③, ②>③
Motor FIM at discharge	61.3±15.7	75.2±7.0	61.0±11.3	72.7±11.5	<0.01	②④>①③
Cognitive FIM at discharge	24.7±7.1	30.0±5.8	22.4±5.8	29.3±5.7	<0.01	②④>①③
Motor benefit of FIM	19.0±11.6	25.7±8.1	21.1±11.6	29.1±11.3	<0.01	④>①③

	①No additional training (n = 45)	②Self-initiated traning (n = 41)	③Training by ward staff (n = 22)	④Dual training (n = 280)	p value†	multiple comparison‡
Motor subscales of FIM at admission 57≦ (n = 388)						
Length of stay	89.3±46.9	69.4±42.4	75.5±33.2	74.6±39.2	0.10	
FTU*	320.7±210.5	251.0±176.3	175.6±78.7	296.0±207.6	0.02	①④>③
FTU/day*	3.5±1.1	3.6±1.0	2.4±0.7	3.9±1.6	<0.01	①②④>③
Motor FIM at admission	71.4±10.3	76.7±9.8	67.3±9.7	70.8±9.2	<0.01	②>③④
Cognitive FIM at admission	27.4±6.3	29.0±5.7	19.8±6.3	29.2±5.9	<0.01	①②④>③