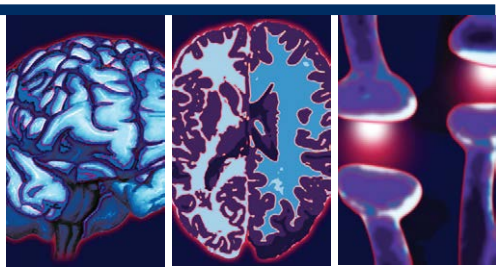

Comparisons of Daily Functional Performance and Relevant Factors in Patients with Alzheimer's Disease and Subcortical Ischemic Vascular Disease

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Abstract

Objective

To compare daily functional performance and potential predictive factors in patients with Alzheimer's disease (AD) and subcortical ischemic vascular disease (SIVD).

Methods

Sixty-eight community patients with AD and 39 with SIVD were evaluated using the informant-based Barthel Index of Activities of Daily Living (B-ADL) and Instrumental Activities of Daily Living (IADL). Motor function, cognition, and white matter hyperintensities (WMHs) were assessed using the modified Rankin Scale (mRS), Cognitive Abilities Screening Instrument (CASI)/Clinical Dementia Rating (CDR), and Scheltens scale, respectively.

Results

After controlling for systemic diseases and medications, toilet use was the only B-ADL subset in which the patients with SIVD performed worse than those with AD in overall comparisons and CDR0.5-1. Additionally, the SIVD group with CDR0.5-1 performed worse in bathing, mobility, and climbing stairs. Regarding IADL performance, the SIVD group had worse performances than the AD group in mode of transportation during CDR2. In WMHs analysis, periventricular WMHs (PWMHs) was the only factor showing significant inverse correlations with both CASI and B-ADL/IADL. Hierarchical regression of all patients suggested that the best models including age, education, PWMHs, CASI, and mRS accounted for 71% and 78% of the variances in B-ADL and IADL, respectively. While mRS accounted for a significant effect in both B-ADL and IADL, CASI accounted for a significant effect only in IADL. Subgroup analysis suggested that the effects of CASI and PWMHs were confined within B-ADL/IADL and IADL in the AD group, respectively.

Conclusions

Motor function was the major factor in both B-ADL and IADL, and cognition had a significant effect on IADL. Although PWMH load had inverse associations with both motor and cognitive functions, this radiological marker better predicted IADL in AD than in SIVD. The variation in daily functional profiles with dementia stage and subtypes highlights the need to assess motor function for preventive interventions.

Keywords

Subcortical ischemic vascular disease; Alzheimer's disease; Cognition; Motor function; Activities of daily life; Instrumental activities of daily life; White matter hyperintensities

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Introduction

Dementia is a syndrome associated with deteriorations in memory, thinking, behavior and the ability to perform everyday activities [1]. Patients with dementia have been shown to exhibit an increasing decline in activities of daily living (ADL) as their cognition deteriorates [2,3]. Moreover, this decline in ADL has been associated with a higher total societal cost and caregiver time [4]. The management of ADL therefore appears to be an important clinical issue, for both a therapeutic and humane care aspect. Two major components of ADL are required to maintain competent autonomy in patients with dementia: basic ADL, defined as abilities related to standard self-care tasks (e.g. eating, using the bathroom, and bathing), and instrumental ADL, which may not be necessary for fundamental functioning but allows for independent living (e.g. housework, financial management, and correct use of medications). As dementia is unanimously associated with the gradual loss of neurons in the central nervous system, the resulting mental and physical disabilities consequently lead to the loss of ADL and decline in life quality.

Several factors in patients with dementia have been associated with impairments in ADL, including cognitive status [5-9], education [9], and white matter hyperintensities (WMHs) [10]. In addition, motor and gait performance have been shown to predict performance of higher-level functioning tasks among the elderly [11]. A more in-depth analysis of these factors and how they are associated could elucidate the fundamental elements of ADL.

There are several subtypes of dementia, of which vascular dementia is the second most common after Alzheimer's disease (AD) in the elderly [12]. In addition, subcortical ischemic vascular disease (SIVD) has been reported to account for a considerable percentage of the patients with clinical vascular dementia [13]. Due to the fact that both AD and SIVD commonly present with a similar, slowly-progressive course of cognitive decline, and as their hallmark pathology may coexist within the same patient, comparisons of daily functional performance may provide additional diagnostic value. Moreover, determining which components of ADL are the most affected in the different stages of dementia in each patient group seems to be of clinical importance, as such knowledge could benefit lifestyle interventions by addressing the point of care strategy [14].

Several studies have reported ADL profiles and their relevant impact among patients with AD [15-17]. However, the functional profiles and determining factors in individuals with SIVD have yet to be fully elucidated [18-20], and comparisons of these two prevalent subtypes of dementia are even more limited [19-20]. Therefore, the aims of the current study were to compare the profiles of ADL performance between patients with SIVD and AD subtypes, and to analyze predictors of daily functional performance in different subtypes of dementia by examining the associations between clinical factors, cognitive/motor function, and WMHs.

Materials and Methods

Sixty-eight community patients with AD and 39 with SIVD who visited the Department of Neurology of our hospital from July 2014 to June 2016 were consecutively recruited. Data on demographics, serology tests, daily function and general cognitive assessments, and brain magnetic resonance imaging (MRI) studies were recorded for each patient. This study was approved by the Institutional Review Board of our hospital (REC 103-14), and all of the participants and their caregivers provided written informed consent to participate in this study.

■ Inclusion and exclusion criteria

The inclusion criteria for the patients with AD were: (1) changes in cognition reported by the patient, informant or clinician [21]; (2) absence of profound subcortical ischemic changes in brain MRI [22]; (3) Clinical Dementia Rating (CDR) of 0.5 ~ 2 [23]; (4) Mini-Mental State Examination (MMSE) score ≤ 26 [24]; and (5) Hachinski Ischemic Scale score ≤ 4 [25]. The inclusion criteria for the patients with SIVD were: (1) cognitive complaints that interfered with complex occupational and social activities [22]; (2) evidence of subcortical ischemic changes in brain MRI [25]; (3) CDR of 0.5 ~ 2 [23]; (4) MMSE score ≤ 26 [24]; and (5) Hachinski Ischemic Scale score ≥ 7 [25]. Subcortical ischemic changes were defined as (i) hyperintensities extending into periventricular and deep white matter; extending caps (>10 mm as measured parallel to the ventricle) or irregular halo (>10 mm with broad, irregular margins and extending into deep white matter) and diffusely confluent hyperintensities (>25 mm, irregular shape) or extensive white matter

changes (diffuse hyperintensity without focal lesions), and lacune(s) in the deep gray matter; or (ii) multiple lacunes (e.g. > 5) in the deep gray matter and at least moderate white matter lesions: extending caps or irregular halo or diffusely confluent hyperintensities or extensive white matter changes [22].

The exclusion criteria were: (1) state of delirium; (2) stroke event within 2 weeks; (3) appearance of cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, hemorrhages, signs of normal pressure hydrocephalus, and specific causes of white matter lesions (e.g. multiple sclerosis, sarcoidosis, brain irradiation) [25]; (4) known serology abnormalities sufficient to impair cognition (e.g. abnormal levels of free T4, cortisol, folic acid, vitamin B12, or rapid plasma reagin); and (5) severe hearing or visual impairment.

■ Demographic data registry

The systemic diseases of all patients were registered. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg in two separate blood pressure measurements [26], a self-reported diagnosis of hypertension, or medical treatment for hypertension. Diabetes mellitus was defined as a fasting blood sugar level ≥ 126 mg/dl, random postprandial blood sugar level ≥ 200 mg/dl, HbA1C ≥ 6.5% [27], a self-reported diagnosis of diabetes mellitus, or treatment with insulin or oral hypoglycemic agents. Chronic kidney disease was defined as a glomerular filtration rate < 60 mL per minute per 1.73 m2 according to the Modification of Diet in Renal Disease Study equation [28] for ≥ 3 months with or without evidence of kidney damage [29]. Coronary artery disease was defined as events and/or history related to stable angina pectoris, unstable angina pectoris, or a myocardial infarction [30]. We included bony fractures and osteoarthritis (regardless of the site) confirmed by an orthopedic specialist or a history of surgery due to orthopedic problems as having orthopedic disease. To avoid the confounding effect of medications on cognitive and daily function performance, the current use (within 1 month) of antipsychotics, anxiolytics, and antidepressants, acetylcholinesterase inhibitors, and memantine was reviewed and recorded.

■ Serology tests

Antecubital venous blood samples were collected after an 8-hour fast for hemogram, serum creatinine, folate, vitamin B12, free T4, thyroid stimulating hormone, cortisol, and rapid plasma reagin measurements. Samples were collected in evacuated tubes containing EDTA, centrifuged within 10 minutes and stored below -20°C until analysis.

■ Daily function assessment

The Barthel Index of Activities of Daily Living (B-ADL) was used to evaluate basic ADL [31]. The B-ADL is a popular assessment tool used to determine how well patients relate to and participate in their environment, with high inter-rater and test-retest reliability [32, 33]. Ten variables describing mobility, including feeding, grooming, toilet use, bathing, dressing, fecal continence (bowel), urinary continence (bladder), mobility, climbing stairs, and transfer (e.g. from a chair to a bed) were rated on this scale with a given number of points assigned to each level or ranking. The amount of time and physical assistance required to perform each task of daily activities were used to determine the value of each variable, which ranged from 0 to 100. The Lawton Instrumental Activities of Daily Living (IADL) Scale [34] is a caregiver-administered instrument designed to measure complex skills needed to successfully live independently. It consisted of eight items: shopping, mode of transportation, food preparation, housekeeping, laundry, ability to use the telephone, responsibility for own medications, and ability to handle finances. The original score is calculated by rating each item dichotomously (0 = less able, 1 = more able) and to then sum the eight responses. However, to fully elucidate the IADL, we scored each item labeled by original descriptions representative of different levels of functioning. Therefore, scoring system of each item has been transformed into a 2 to 4 point system, and the total score therefore ranged from 0 to 24. Higher scores in both the B-ADL and IADL represented lower levels of dependence. Together, the B-ADL and IADL represent the skills that people usually need to be able to manage in order to live as independent adults. Both the B-ADL and IADL were completed by a single nursing practitioner (YQ Yu) after the informants received appropriate instructions and while the patients were present at the clinic so that they could provide additional information when needed.

■ Motor function assessment

Motor function was evaluated using the modified Rankin Scale (mRS). The mRS is a scale

commonly used in patients with cerebrovascular disease [35] to reflect disabilities related to cerebrovascular disease pathology. A higher mRS score indicates a state of greater debilitation as described below:

0 = No symptoms at all.

1 = No significant disability despite symptoms; able to carry out all usual duties and

activities.

2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.

3 = Moderate disability; requiring some help, but able to walk without assistance.

4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.

5 = Severe disability; bedridden, incontinent and requiring constant nursing care and

attention.

6 = Dead.

■ Cognitive function assessment

General cognitive evaluations included the CDR [23], the Taiwanese version of the MMSE [24], and Cognitive Abilities Screening Instrument (CASI) [36]. The CDR is a semi-structured interview performed with the patient and a reliable informant. A CDR score of 0 denotes no cognitive impairment, with the remaining four scores representing various stages of severity (0.5: very mild; 1: mild; 2: moderate; 3: severe) [23]. Both the MMSE and CASI assess global cognition of the subject, with a higher score representing better cognition.

■ Brain MRI

Brain MRI was performed in all patients using a 3.0T scanner (Discovery MR750, GE Medical System, Milwaukee, WI). WMHs were rated in accordance with the Scheltens scale [37] from T2-fluid-attenuated inversion recovery (T2-FLAIR) sequences in an axial plane by a single rater (MC Tu). The parameters were as follows: repetition time 12000 msec, echo time 120 msec, inversion time 2200 msec, slice thickness 5 mm, field of view 24 cm, and matrix 256 x 256. The Scheltens scale is a semi-quantitative visual rating method for WMHs with good intra- and inter-observer reliability [37]. In our analysis of both the number and volume of WMHs, anchored 2-, 7-, and 7-point severity ratings were applied in periventricular WMHs (PWMHs) (i.e., frontal horn, occipital horn, and lateral bands), deep WMHs (DWMHs) (i.e., frontal, temporal, parietal and occipital lobes), and basal ganglia (i.e., caudate nucleus, putamen, globus pallidus, internal capsule and thalamus) regions, respectively. We did not assess infratentorial regions due to their limited impact on cognition.

■ Statistical analysis

The independent T test and $\chi 2$ test were used to detect group differences in demographic data, daily/cognitive function assessments and WMHs where appropriate. Analysis of covariance (ANCOVA) was used to compare group differences controlling for possible covariates, and Pearson's correlation analysis was used to evaluate associations between daily functions, cognitive test scores and WMHs. To determine the impact of each individual factor of interest, hierarchical multiple regression analyses were conducted. All statistical tests were performed using SPSS software version 19 (IBM, Armonk, New York). A p value less than 0.05 was considered to be statistically significant.

Results

■ Demographic data

Table 1 shows the demographic data of the patients with AD and SIVD. Overall, there were no significant differences between the groups in age, gender, education, or disease duration ($p = 0.268 \sim 0.941$). The patients with SIVD had higher Hachinski Ischemic Scale and mRS scores (both $p < 0.001$), and a higher prevalence of several systemic diseases including cerebrovascular disease ($p < 0.001$), hypertension ($p = 0.022$), and diabetes mellitus ($p = 0.048$). There was no significant difference in the prevalence of orthopedic disease between the two groups ($p = 0.143$). With regards to medications, the patients with SIVD had a higher rate of antidepressant use ($p = 0.032$) and a lower rate of acetylcholinesterase inhibitor use ($p < 0.001$) than the patients with AD. Subgroup comparisons by CDR severity showed that the patients with SIVD with CDR 0.5-1 and CDR 2 had higher Hachinski ischemic scale ($p < 0.001$) and mRS ($p < 0.01 \sim 0.05$) scores than those with AD. The patients with SIVD and CDR 0.5-1 had a higher prevalence of cerebrovascular disease ($p = 0.001$), and a lower rate of acetylcholinesterase inhibitor treatment

Table 1: Comparisons of demographic data between the patients with Alzheimer's disease and subcortical ischemic vascular disease.

	AD			SIVD		
	Overall (*n* = 68)	CDR 0.5-1 (*n* = 48)	CDR 2 (*n* = 20)	Overall (*n* = 39)	CDR 0.5-1 (*n* = 26)	CDR 2 (*n* = 13)
Age (years-old)	76.9 (9.35)	74.7 (9.03)	82.2 (7.99)	77.0 (7.88)	77.2 (7.84)	76.7 (8.26)
Gender (Male/Female)	24/44	18/30	6/14	17/22	12/14	5/8
Education (years)	5.2 (4.58)	5.3 (4.53)	5.0 (4.82)	4.9 (3.89)	4.5 (3.59)	5.6 (4.48)
Hachinski Ischemic Scale	0.7 (0.91)	0.6 (0.87)	0.8 (1.02)	5.7 (1.00)***	5.7 (0.96)###	5.7 (1.11)§§§
Modified Rankin Scale	1.5 (1.70)	0.7 (1.04)	3.4 (1.46)	2.8 (1.92)***	2.0 (1.89)##	4.3 (0.75)§
Disease duration (years)	2.4 (1.46)	1.7 (0.97)	4.1 (1.00)	2.5 (1.57)	1.6 (1.07)	4.3 (0.48)
Cognitive Abilities Screening Instrument	51.8 (21.88)	61.5 (16.29)	28.6 (15.02)	49.3 (16.90)	54.6 (13.56)	38.5 (18.30)
Mini-Mental State Examination	16.4 (6.89)	19.3 (5.41)	9.3 (4.46)	15.8 (5.37)	17.6 (4.48)	12.0 (5.27)
Clinical Dementia Rating _sum of box	6.6 (4.12)	4.4 (2.43)	12.0 (1.49)	6.6 (3.83)	4.3 (2.32)	11.2 (1.28)
Systemic diseases (*n*) - Cerebrovascular disease	7	4	3	16***	11##	5
- Hypertension	23	18	5	21*	14	7
- Diabetes mellitus	10	9	1	12*	8	4
- Chronic kidney disease	12	9	3	7	3	4
- Orthopedic disease	7	4	3	8	4	4
Medication (*n*) - Antipsychotics	3	1	2	1	0	1
- Benzodiazepine	10	7	3	3	1	2
- Antidepressants	8	4	4	11*	6	5
- Acetylcholinesterase inhibitor	33	27	6	0***	0###	0
- Memantine	4	0	4	0	0	0

(1) Abbreviation: SIVD = subcortical ischemic vascular disease, AD = Alzheimer's disease (2) independent T-test and Chi-square test were used to evaluate the group difference where appropriate; significant difference was defined as *p* value < 0.05. (3) *: $p < 0.05$; ***: $p < 0.001$ on the comparisons between all SIVD patients and all AD patients;#: $p < 0.05$; ##: $p < 0.01$; ###: $p < 0.001$;on the comparisons between SIVD and AD patients with CDR score = 0.5-1; §: $p < 0.05$, §§§: $p < 0.001$ on the comparisons between SIVD and AD patients with CDR score = 2.

($p < 0.001$). There were no significant differences in other demographic factors including age, gender, and cognition between the two groups ($p = 0.070 \sim 0.892$).

■ Comparisons of daily function

Table 2 shows comparisons of B-ADL profiles between the patients with AD and SIVD. Overall, the patients with SIVD had lower achievements of daily function in all variables of the B-ADL except for feeding and grooming ($p < 0.05 \sim 0.001$). Sub-group comparisons by dementia stage suggested that the patients with SIVD had significantly lower B-ADL total scores than the patients with AD across different stages of dementia ($p < 0.05 \sim 0.001$). Among the patients with CDR 0.5-1, those with SIVD had a significantly lower achievement in toilet use, bathing, dressing, mobility, climbing stairs, and transfer ($p < 0.05 \sim 0.01$). Among the patients with CDR 2, those with SIVD had significantly lower scores of bowel and bladder continence in addition to toilet use and bathing ($p < 0.05 \sim 0.01$). After controlling for systemic diseases and medications, the patients with SIVD still had lower B-ADL scores overall and when they had a CDR of 0.5-1 ($p < 0.05$). Scores of toilet use, bathing, mobility, and climbing stairs were significantly lower among the patients with a CDR of 0.5-1 and SIVD than in those with a CDR of 0.5-1 and AD ($p < 0.05 \sim 0.01$). There were no significant differences in B-ADL scores between the two groups with a CDR of 2. After controlling for systemic diseases, medications, and mRS, toilet use remained the only item in which the patients with SIVD performed worse than those with AD overall ($p = 0.002$) and in those with a CDR of 0.5-1 ($p = 0.008$).

With regards to the progression of B-ADL performance between the patients in the two groups, the scores of all variables of the B-ADL significantly declined as the stage of dementia progressed in the patients with AD ($p < 0.05$), and also in the patients with SIVD ($p < 0.05$) except for feeding and transfer.

Table 3 shows comparisons of IADL profiles between the two groups. Overall, the patients with SIVD had lower IADL scores due to lower achievements in mode of transportation, food preparation, housekeeping, laundry, and responsibility for own medications ($p < 0.05 \sim 0.01$). In addition, lower achievements in IADL total scores, food preparation, housekeeping,

Table 2: Comparisons of the Barthel Index of Activities of Daily Living between the patients with Alzheimer's disease and subcortical ischemic vascular disease.

	AD			SIVD			*P* value in AD vs. SIVD after controlling for systemic diseases and medications.		
	Overall (*n* = 68)	CDR0.5-1 (*n* = 48)	CDR2 (*n* = 20)	Overall (*n* = 39)	CDR0.5-1 (*n* = 26)	CDR2 (*n* = 13)	Overall (*n* = 68 *vs.*39)	CDR0.5-1 (*n* = 48 *vs.*26)	CDR2 (*n* = 20 *vs.* 13)
ADL total score†‡	87.1 (17.56)	95.5 (7.16)	67.0 (18.88)	66.8 (29.28)***	77.1 (26.05)##	46.2 (24.68)§	***0.030***	***0.011***	0.198
Feeding†	9.6 (1.67)	10.0 (0.00)	8.5 (2.86)	9.4 (2.05)	9.8 (0.98)	8.5 (3.15)	0.914	0.530	0.359
Grooming†‡	4.5 (1.53)	5.0 (0.00)	3.3 (2.45)	3.9 (2.13)	4.6 (1.36)	2.3 (2.59)	0.222	0.352	0.249
Toilet use†‡	9.2 (2.11)	9.9 (0.72)	7.3 (3.02)	6.5 (3.66)***	7.9 (3.22)##	3.9 (3.00)§§	***0.001***	***0.001***	0.058
Bathing†‡	3.7 (2.22)	4.8 (1.01)	1.0 (2.05)	2.1 (2.49)**	3.1 (2.48)##	0.0 (0.00)§	0.111	***0.021***	0.994
Dressing†‡	8.4 (2.75)	9.6 (1.40)	5.6 (3.12)	6.4 (3.80)**	7.7 (3.23)##	3.9 (3.63)	0.193	0.079	0.682
Bowels†‡	9.3 (1.98)	9.8 (1.01)	8.0 (2.99)	7.7 (3.21)**	9.2 (1.84)	4.6 (3.20)§§	0.352	0.476	0.260
Bladder†‡	9.0 (2.16)	9.7 (1.22)	7.5 (3.03)	7.4 (3.42)**	9.0 (2.01)	4.2 (3.44)§§	0.265	0.473	0.127
Mobility†‡	13.8 (2.18)	14.5 (1.54)	12.0 (2.51)	10.9 (5.11)**	11.9 (4.49)##	9.9 (5.83)	0.101	***0.019***	0.442
Stairs†‡	7.2 (3.80)	8.8 (2.42)	3.5 (4.01)	4.2 (4.67)**	5.6 (4.76)##	1.5 (3.15)	0.178	***0.031***	0.763
Transfer†	12.5 (2.93)	13.5 (2.30)	10.0 (2.81)	10.5 (4.70)*	11.5 (4.42)#	8.5 (4.74)	0.627	0.188	0.632

(1) Abbreviation: SIVD = subcortical ischemic vascular disease, AD = Alzheimer's disease, ADL = activities of daily living (2) T-test was used to evaluate the group difference and significant difference was defined as *p* value < 0.05. (3) *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ on the comparisons between all SIVD patients and all AD patients;#: $p < 0.05$; ##: $p < 0.01$ on the comparisons between SIVD patients and AD patients with CDR score = 0.5-1; §: $p < 0.05$, §§: $p < 0.01$ on the comparisons between SIVD and AD patients with CDR score = 2. (4) £: $p < 0.05$ and ££: $p < 0.01$ on the comparisons between patient with CDR score = 0.5 and with CDR score = 1 ~ 2 among all patients respectively. (5) †: $p < 0.05$ on the comparisons between patient with CDR score = 0.5-1 and with CDR score = 2 in AD group. (6) ‡: $p < 0.05$ on the comparisons between patient with CDR score = 0.5-1 and with CDR score = 2 in SIVD group. (7) *P* values (resulted from ANCOVA) in comparison between AD and SIVD with variable stages after the adjustment for both systemic diseases and medications; *P* values < 0.05 are boldly italicized.

Table 3: Comparisons of the Instrumental Activities of Daily Living between the patients with Alzheimer's disease and subcortical ischemic vascular disease.

	AD			SIVD			*P* value in AD vs. SIVD after controlling for systemic diseases and medications.		
	Overall (*n* = 68)	CDR0.5-1 (*n* = 48)	CDR2 (*n* = 20)	Overall (*n* = 39)	CDR0.5-1 (*n* = 26)	CDR2 (*n* = 13)	Overall (*n* = 68 vs.39)	CDR0.5-1 (*n* = 48 vs.26)	CDR2 (*n* = 20 vs. 13)
IADL total score†‡	12.9(6.93)	16.2 (5.37)	5.1 (2.11)	9.6 (7.06)*	12.2 (7.17) #	4.3 (2.39)	0.928	0.307	0.481
Shopping†‡	1.6 (0.95)	2.0 (0.87)	0.8 (0.44)	1.3 (0.94)	1.6 (0.99)	0.7 (0.48)	0.713	0.770	0.493
Mode of transportation†‡	2.1 (1.39)	2.5 (1.44)	1.0 (0.00)	1.5 (1.25)*	1.9 (1.41)	0.9 (0.38)	0.445	0.190	***0.016***
Food preparation†‡	1.4 (1.31)	1.9 (1.19)	0.1 (0.45)	0.7 (1.27)*	1.1 (1.42) #	0.0 (0.00)	0.682	0.613	0.346
Housekeeping†‡	2.6 (1.24)	3.2 (0.88)	1.2 (0.75)	1.7 (1.36)**	2.2 (1.35) ##	0.9 (0.90)	0.313	0.058	0.605
Laundry†‡	1.2 (0.96)	1.6 (0.77)	0.2 (0.49)	0.7 (0.97)*	1.0 (1.00) #	0.2 (0.56)	0.413	0.982	0.698
Ability to use telephone†‡	1.7 (1.01)	2.2 (0.81)	0.8 (0.72)	1.5 (1.12)	2.0 (1.04)	0.7 (0.75)	0.893	0.905	0.435
Responsibility for own medications†‡	1.8 (0.81)	2.1 (0.79)	1.2 (0.37)	1.4 (0.75)*	1.7 (0.80) #	1.0 (0.41)	0.476	0.220	0.169
Ability to handle finances†‡	0.7 (0.68)	1.0 (0.62)	0.1 (0.22)	0.6 (0.72)	0.7 (0.73)	0.1 (0.28)	0.301	0.673	0.219

(1) Abbreviation: SIVD = subcortical ischemic vascular disease, AD = Alzheimer's disease, IADL = instrumental activities of daily living scale (2) T-test was used to evaluate the group difference and significant difference was defined as *p* value < 0.05. (3) *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ on the comparisons between all SIVD patients and all AD patients; ;#: $p < 0.05$; ##: $p < 0.01$; ###: $p < 0.001$ on the comparisons between SIVD patients and AD patients with CDR score = 0.5-1 (4) £: $p < 0.05$ and ££: $p < 0.01$ on the comparisons between patient with CDR score = 0.5 and with CDR score = 1 ~ 2 among all patients respectively. (5) †: $p < 0.05$ on the comparisons between patient with CDR score = 0.5-1 and with CDR score = 2 in AD group. (6) ‡: $p < 0.05$ on the comparisons between patient with CDR score = 0.5-1 and with CDR score = 2 in SIVD group. (7) *P* values (resulted from ANCOVA) in comparison between AD and SIVD with variable stages after the adjustment for both systemic diseases and medications; *P* values < 0.05 are boldly italicized.

laundry, and responsibility for own medications were noted among the patients with SIVD and a CDR of 0.5-1 ($p < 0.05 \sim 0.01$) but not CDR 2. After controlling for systemic diseases and medications, mode of transportation in the patients with SIVD and CDR 2 was the only significantly lower performance in pairwise comparisons with the patients with AD ($p < 0.05$). We further added mRS as a covariate in addition to systemic diseases and medications

to control for the effect of motor ability, and the results showed that the patients with SIVD had worse performances than those with AD in laundry ($p = 0.014$) and the ability to handle finances ($p = 0.027$) overall, and in mode of transportation when they had a CDR of 2 ($p = 0.021$). With regards to changes in IADL performance, all variables of the IADL declined as the stage of dementia progressed in both groups ($p < 0.05$).

■ Correlations among cognition, daily and motor function, and WMHs

Table 4 shows correlations among cognition (total scores of the MMSE and CASI), daily function (total scores of the B-ADL and IADL), motor function (mRS), and WMHs (total scores of WMHs and each segregated region). There were significantly positive correlations among each index of cognition and daily function (all $p < 0.01$). In addition, mRS scores showed significant inverse correlations with all indices of cognition and daily function (all $p < 0.01$) and positive correlations with the WMHs in all segregated regions ($p < 0.01 \sim 0.05$). There were also significant inverse correlations between B-ADL and the WMHs in all segregated regions (all $p < 0.01$). However, the total scores of WMHs, PWMHs, DWMHs, but not WMHs within basal ganglia, were inversely correlated with total IADL scores. Of note, only PWMH scores were inversely correlated with cognitive performance ($p < 0.01 \sim 0.05$).

■ Hierarchical multiple regression analysis

Table 5 shows hierarchical multiple regression analysis conducted with all participants and each individual dementia subtype. As PWMHs were the only index significantly correlated with cognition and daily function performance, PWMHs were chosen to be an independent variable in regression analysis. Hierarchical multiple regression analysis was conducted to examine the roles of the targeted factors on ADL. The independent variables included age, education, PWMHs, mRS (motor function), and CASI (cognitive function), and the dependent variables were total scores of the B-ADL and IADL.

In step 1, two demographic variables (age and education) were included. This model was designed to control for the potential effect of the demographic factors on ADL. Overall (AD + SIVD; n = 107), Model 1 significantly predicted the total scores of both the B-ADL ($p = 0.005$) and IADL ($p < 0.001$), accounting for 10% and 22% of the variance for B-ADL and IADL, respectively. Age accounted for a significant effect in both the B-ADL ($p = 0.003$) and IADL ($p < 0.001$).

Step 2 included PWMHs in addition to demographic factors. PWMHs accounted for a significant effect on the B-ADL (6% of variance; standardized $\beta = -0.262$; $p = 0.006$) and IADL (9% of variance; standardized $\beta = -0.306$; $p < 0.001$), after controlling for the aforementioned demographic factors.

Step 3 involved the results of stepwise regression analysis including mRS and CASI scores, and all variables in Step 2, in order to examine the proportional effect of motor and cognitive function after controlling for demographic factors and PWMH load. Step 3 accounted for a significant proportion of variance in both the B-ADL and IADL ($\Delta R2 = 0.551$, $p < 0.001$ in the B-ADL; $\Delta R2 = 0.474$, $p < 0.001$ in the IADL). While mRS accounted for a significant effect in both the B-ADL and IADL, the CASI accounted for a significant effect only in the

Table 4: Correlations among white matter hyperintensities, cognition, motor function, and activities of daily living.

	CASI	MMSE	ADL	IADL	mRS	PWMHs	DWMHs	BG	Total score
CASI		0.961**	0.385**	0.602**	- 0.475**	- 0.233*	- 0.185	0.025	- 0.130
MMSE			0.378**	0.594**	- 0.473**	- 0.252**	- 0.186	0.017	- 0.137
B-ADL				0.683**	- 0.829**	- 0.317**	- 0.341**	- 0.322**	- 0.375**
IADL					- 0.838**	- 0.398**	- 0.341**	- 0.184	- 0.332**
mRS						0.346**	0.319**	0.233*	0.331**
PWMHs							0.775**	0.594**	0.847**
DWMHs								0.588**	0.918**
BG									0.846**

Abbreviation: CASI = Cognitive Abilities Screening Instrument; MMSE = Mini-mental state examination; B-ADL = Barthel Index of Activities of Daily Living; IADL = Instrumental Activities of Daily Living Scale; mRS = modified Rankin Scale; PWMHs = periventricular white matter hyperintensities; DWMHs = deep white matter hyperintensities; BG = basal ganglia hyperintensities; Total score = PWMHs + DWMHs + BG. *: $p < 0.05$; **: $p < 0.01$.

Table 5: Hierarchical multiple regression analysis of possible factors for activities of daily living.

	B-ADL					IADL				
Variable entered	***β***	**95%CI**	***P* value**	**R^2**	**ΔR^2**	***β***	**95%CI**	***P* value**	**R^2**	**ΔR^2**
All patients (*n* = 107)										
Step 1			***.005***	.097	-			***< .001***	.218	
Age	- .296	(-1.352,- .294)	***.003***			- .476	(- .529, - .243)	***< .001***		
Education	- .187	(-2.133, .018)	.054			- .051	(- .375, .208)	.569		
Step 2			***.006***	.161	.064			***< .001***	.306	.088
Age	- .226	(-1.159, - .098)	***.021***			- .394	(- .460, - .179)	***< .001***		
Education	- .176	(- 2.041, .044)	.060			- .039	(- .340, .213)	.649		
PWMHs	- .262	(- 6.182, - 1.064)	***.006***			- .306	(- 1.914, - .558)	***< .001***		
Step 3			***< .001***	.712	.551			***< .001***	.781	.474
Age	.052	(- .190, .479)	.394			- .123	(- .185,- .014)	***.022***		
Education	- .142	(- 1.443, -.161)	***.015***			- .057	(- .257, .069)	.255		
PWMHs	- .040	(- 2.127, 1.029)	.492			- .098	(- .796, .006)	.054		
mRS	- .818	(- 12.296, -8.924)	***< 0.001***			- .641	(- 2.850,- 1.993)	***< .001***		
CASI	.045	(- .101, .209)	.490			.248	(.048, .127)	***< .001***		
AD patients (*n* = 68)										
Step 1			***.001***	.190	-			***< .001***	.274	-
Age	-.444	(-1.262, -.405)	***< 0.001***			-.524	(-.547, -.228)	***< .001***		
Education	-.131	(-1.373, .373)	.257			-.004	(-.332, .319)	.967		
Step 2			.591	.194	.004			***.005***	.357	.084
Age	-.418	(-1.251, -.320)	***.001***			-.402	(-.461, -.134)	***.001***		
Education	-.134	(-1.391, .367)	.249			-.019	(-.338, .280)	.851		
PWMHs	-.066	(-3.206, 1.841)	.591			-.315	(-2.168, -.395)	***.005***		
Step 3			***< .001***	.842	.648			***< .001***	.789	.431
Age	-.006	(-.245, .221)	.920			-.109	(-.187, .025)	.132		
Education	-.156	(-1.009, -.187)	***.005***			-.089	(-.321, .052)	.155		
PWMHs	.082	(-.337, 2.204)	.158			-.154	(-1.162, -.087)	***.023***		
mRS	-.824	(-9.935, -7.132)	***< 0.001***			-.483	(-2.608, -1.332)	***< .001***		
CASI	.189	(.046, .258)	***.006***			.387	(.074, .171)	***< .001***		
SIVD patients (*n* = 39)										
Step 1			.072	.136	-			***.030***	.177	-
Age	-.237	(-2.109,.344)	.153			-.439	(-.682, -.105)	***.009***		
Education	-.364	(-5.228,-.258)	***.031***			-.179	(-.909, .260)	.268		
Step 2			.830	.137	.001			.732	.180	.003
Age	-.234	(-2.120,.380)	.166			-.434	(-.683, -.095)	***.011***		
Education	-.353	(-5.303, -.010)	***.049***			-.161	(-.914, .330)	.347		
PWMHs	-.036	(-7.718, 6.229)	.830			-.055	(-1.918, 1.361)	.732		
Step 3			***< .001***	.601	.464			***<.001***	.817	.637
Age	-.022	(-1.024,.861)	.861			-.192	(-.326, -.018)	***.030***		
Education	-.224	(-3.607, .240)	.084			-.004	(-.322, .306)	.959		
PWMHs	.010	(-4.757, 5.176)	.932			.002	(-.801, .822)	.980		
mRS	-.714	(-14.680, -7.065)	***< .001***			-.845	(-3.725, - 2.481)	***<.001***		
CASI	.010	(-.437, .472)	.938			-.015	(-.080, .068)	.865		

P values < 0.05 are boldly italicized. Abbreviation: CASI = Cognitive Abilities Screening Instrument; mRS = modified Rankin Scale; B-ADL = Barthel Index of Activities of Daily Living; IADL = Instrumental Activities of Daily Living Scale; PWMHs = periventricular white matter hyperintensities.

IADL. In summary, the final model accounted for 71% of the variance in B-ADL and 78% variance in IADL.

We then conducted another two separate hierarchical multiple regression analyses using the same procedure with either patients with AD or those with SIVD (Table 5). Among the patients with AD (n = 68), PWMHs still had a significant predictive value for IADL (standardized β = - 0.315; p = 0.005) but not B-ADL (p = 0.591) after controlling for age and education. In the final model, both mRS (standardized β = - 0.483 and 0.824; both p < 0.001) and CASI (standardized β = 0.189 and 0.387; p = 0.006 and < 0.001) still accounted

for significant proportions of variance in both the B-ADL and IADL after controlling for age, education, and PWMHs.

In contrast to the findings in the patients with AD, the mRS score had a significant predictive value for the B-ADL and IADL (standardized β = - 0.714 and - 0.845; both $p < 0.001$) in the patients with SIVD (n = 39) after controlling for age, education, and PWMHs in the final model. In addition, the significant effect of PWMHs was not observed in this regression analysis (p = 0.980 ~ 0.732).

Discussion

This study found distinct differences in the severity and profiles of daily functional performance between the patients with AD and SIVD, which may have been due to the variable impact of mental/physical disabilities and WMHs. Aside from cognitive and motor function; PWMHs were significant predictors of daily functional performance. In addition, this impact appeared to be more evident among the patients with AD compared to those with SIVD.

Although the original data suggested worse performance in almost all variables of both the B-ADL and IADL in the patients with SIVD compared to those with AD, the fully adjusted model indicated that the patients with SIVD had worse performance in toilet use in the B-ADL and laundry and the ability to handle finances in the IADL than those with AD. These results suggest different complexities and cognitive demand between specific items of the B-ADL and IADL. For example, whereas motor function was identified to be a major contributing factor to both the B-ADL and IADL, cognitive function appeared to be of greater importance in the IADL. These findings are consistent with previous studies in which variable cognitive demand was reported among different daily function tasks [38].

A possible explanation for the different ADL profiles between the SIVD and AD groups is their disparate pattern of cognitive impairments. Activities including toilet use, laundry, and the ability to handle finances are usually of greater task complexity and are associated with a higher level of executive function, as they all require initial planning and execution of multiple-step sequences. Executive function involves manipulation and update of incoming stimuli through working memory [39], and governs tasks that are conducted in a proper sequence by sustaining attention and monitoring feedback [40]. Previous studies have suggested that patients with vascular dementia/SIVD have worse executive function than those with AD [19, 41], and that such discernible changes may even be identified during the very early stage [42]. Other studies have suggested that patients with SIVD have greater deficits in working memory and visuomotor speed compared to patients with AD [43]. Taken together, we hypothesize that executive dysfunction among patients with SIVD may preferentially lead to a worse performance in multi-step tasks compared to patients with AD.

Another explanation for the distinct B-ADL/IADL profiles between patients with SIVD and AD may be differences in motor function disability. The patients with SIVD in this study had higher rates of cerebrovascular disease and associated risk factors, and thereby worse physical capacity than those with AD, as evidenced by a higher mRS among the patients with SIVD. Of note, motor function exerted a consistently significant effect across dementia subtypes and B-ADL/IADL in this study. Moreover, the significant correlations between motor and cognitive function in this study also highlight the possibility that both of these functions play important roles in the performance of ADL. Therefore, regular measurements of motor function may be as important as cognitive function in long-term care programs. This observation is consistent with research examining the association between gait and cognition, and a decline in gait speed has been reported to predate the clinical diagnosis of dementia [44] and to be a strong predictor of dementia [45]. A growing body of evidence also supports that physical activity has a positive impact on cognition and vice versa [46]. Specifically, cognitive implementation involving execution, including spatial perception, attention, and working memory, is regarded to be important for gait [46, 47], as these cognitive domains represent neuronal networks with a considerable overlap with fronto-subcortical circuits, thereby affecting gait performance.

Our study results provide an interesting parallel with previous studies. In one study recruiting patients with AD and SIVD, the patients with SIVD had a worse performance on the B-ADL but not on the IADL compared to the patients with AD on the basis of comparable MMSE, CDR, and CDR sum-of-box scores [19]. The authors

therefore concluded that patients with SIVD have greater physical dependency than those with AD under a comparable general cognitive status. However, worse executive function and a more profound severity of depression, as evident among the patients with SIVD in that cohort, may also have contributed to their performance on the B-ADL [19]. Another study suggested that nearly all items of the B-ADL and IADL tasks involving physical activities were most affected by WMH load in patients with AD or SIVD [48]. However, subgroup differences in the demographic and cognitive profiles are likely to have confounded their results, and correlations between WMHs and IADL were also lacking [48]. As cognition, motor status, and WMHs tend to show considerable interactions, our study is a comprehensive examination of the proportional impact of each factor with regards to their contribution to ADL.

It is also noteworthy that the distinguishing activities between these two subtypes of dementia varied according to the severity of dementia. During the early stage, the patients with SIVD were prone to have worse performance in toilet use, bathing, mobility, and climbing stairs than those with AD. This underpins the necessity of early interventions for environmental safety with regards to bathroom and stair usage. Impedance of toilet use and bathing are major care problems among patients with dementia [49, 50], and they are associated with compromised dignity and autonomy. The causes are multifactorial, and include a poor access of design, visibility and restricted space in a toilet, distractions, and even unfamiliar or fearful feelings toward the equipment [51]. Similarly, poorly designed steps and handrails as well as non-clearly defined edges can lead to injuries related to the use of stairs [52]. Our results reflect the fact that patients with SIVD are prone to have more difficulties with activities specifically conducted in bathrooms and climbing stairs. Therefore, maximizing visual access, controlling levels of simulation, and using safety measures may be beneficial for patients with SIVD on the basis of their underlying cognitive and motor deficits [53]. During the later stage, the patients with SIVD tended to show worse performance in the mode of transportation than those with AD. This is consistent with a previous study in which the volume of WMHs was a significant and independent predictor of gait performance among the elderly [54].

Our study also highlights the negative impact of PWMHs on cognition among patients with dementia, and that it is more profound among patients with AD. Several lines of evidence support the role of coexisting vascular pathologies in the cognitive function of elderly or demented patients. In a study of carotid ultrasonography, carotid atherosclerosis was a predictive factor for the progression of cognitive impairment in patients with AD [55]. In addition, apart from the occurrence of a clinical stroke, an epidemiology report highlighted associations between vascular risk factors including hypertension, diabetes mellitus, atrial fibrillation, and even silent infarct with the risk for subsequent dementia or cognitive decline [56]. A comprehensive brain autopsy study also reported the role of vascular burden in cognition, where micro infarcts were specifically associated with lower episodic memory, semantic memory, and perceptual speed in addition to global cognitive deficits [57]. PWMHs and DWMHs have been reported to have overlapping but different histopathological and functional correlates. In postmortem studies, PWMHs have been shown to represent discontinuous ependyma, gliosis, loosening of the white matter fibers, and myelin loss, whereas DWMHs have been shown to involve greater axonal loss, vacuolation, and infarction in addition to demyelination and gliosis [58, 59]. Although some studies have suggested that both contribute to cognitive decline in the ageing process [60], others have proposed that PWMHs [61-63] or DWMHs [64] are significant predictors of cognitive outcomes. Those inconsistencies may be biased by variable anatomical definitions for PWMHs and DWMHs. However, an imaging study comparing different criteria still concluded that PWMHs were more strongly associated with reduced cognitive function, higher mean arterial pressure and age than DWMHs [65]. In one study on the impact of WMHs in patients with AD, PWMHs but not DWMHs were independently correlated with reductions in hippocampal volume, and they were also associated with worse B-ADL and cognitive performance [61]. Furthermore, studies enrolling patients with amnestic mild cognitive impairment have identified the role of PWMHs in IADL and executive function [62], and a higher PWMH load in patients with the single-domain subtype than in those with multi-domain subtypes [66]. On the basis that PWMHs but not DWMHs are strongly correlated with cognitive scores and the B-ADL/IADL, we suggest that PWMHs have a distinct

clinical impact not only on cognition, but also ADL status.

The strength of our research includes the study design with structured functional/cognition evaluations on the basis of standardized MRI assessments. The subgroup comparisons also demonstrated the results according to the subtype and severity of dementia. Knowledge of these factors may be helpful in improving the quality of life of patients with AD and SIVD. However, there are also several limitations to this study. First, the diagnosis of the current cohort relied mainly on criteria from a clinicoradiological basis. Therefore, to incorporate biomarkers, especially those related to AD pathology (e.g., cerebrospinal fluid tau protein and Abeta42), may have further confirmed our major findings. Second, due to the fact that the impact of cognition on ADL may be affected by motor status, performance-based measurements (e.g., the Taiwan Performance-Based IADL) [67] may be an alternative method to further clarify the cognition-ADL association. There is concern that using mRS to be a single index of motor function may not totally reflect disability resulted from non-cerebrovascular disease. Due to the fact that a considerable portion of patients have SIVD and/or cerebrovascular disease, we are convinced that using the mRS could reliably represent the overall functional status. Third, although our study highlighted the clinical importance of PWMHs on the functional performance of patients with AD, the impact of PWMHs was not documented in those with SIVD. The results did not negate the role of WMHs among the patients with SIVD, as the fundamental pathogenesis of SIVD including microstructural changes and cerebral blood flow may not be fully surrogated by the assessment of WMHs in conventional MRI. In other words, the assessment of WMHs may have a ceiling effect and therefore attenuate its impact on functional status performance among patients with SIVD. Another possible explanation is that patients with SIVD have a more profound fiber disconnection state than those with AD [68], raising the possibility that associations between PWMHs and executive function may vary according to the subtype of dementia. Incorporating other WMH scales specific for cholinergic pathways [69], or other novel sequences measuring cerebral microstructural [68] and blood flow changes [70] should be considered for future studies.

Conclusions

This study demonstrated variations in the profiles of daily functional performance with the stage and subtype of dementia. The patients with SIVD had worse performance in multiple B-ADL/IADL tasks than those with AD, even during the early stage of dementia. These findings provide valuable information regarding early non-pharmacological ADL interventions among patients with SIVD, and highlight the importance of preventive therapy aimed at reducing cerebrovascular risk factors among the elderly. The construct properties between the B-ADL and IADL were different, as evidenced by their different proportion of motor/cognitive function and WMHs to be their responsible factors. In the patients with dementia overall, motor function played a major factor in both the B-ADL and IADL, and cognition had a significant effect on the IADL. Therefore, regular measurements of motor function may be as important as cognitive function in long-term care programs. Although PWMH load had inverse associations with both motor and cognitive function, its effect was more profound among the patients with AD than those with SIVD. The results underscore the importance of observing any symptoms of a decline in the IADL and controlling modifiable vascular risk factors among patients with AD and coexisting PWMHs.

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