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Cognitive and functional progression of Alzheimer's disease patients in Singapore and their short-term prognosis

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INTRODUCTION

Dementia is a major public health issue in Singapore, which has one of the fastest ageing populations in the Asia Pacific region. The number of patients with dementia (PWD) is expected to rise to 55,000 locally by the year 2020.[1] It is among the largest drains on Singapore's healthcare system, with an economic cost amounting to $1.4 billion every year.[2]

The rise in number of PWD on the back of a silver tsunami brings forth significant concerns regarding the burden of care for these patients. A shrinking number of family members available to care for their ageing demented parents, coupled with a high caregiver burden among caregivers of PWD, has led to an increase in demand for long-term institutional care, evidenced by the anticipated expansion in nursing home capacity by 50% over the next decade.[3]

Dementia is one of the main reasons for institutional care. Alzheimer's disease (AD) is the most common form of dementia.[4] Most elderly PWD live in the community with their families, and thus the burden of care lies heavily on relatives. Often, relatives experience emotional stress, and have to discontinue their daily routines when caring for a PWD, resulting in a high caregiver burden, which strongly influences time and desire to institutionalisation.[5] Other predictors include increased global severity of dementia at onset, presence of disruptive behavioural and psychological symptoms of dementia (BPSD),[6] as well as incontinence.[7]

There is limited local data on the short-term prognosis of PWD in terms of institutionalisation or function within the community. The median time to institutionalisation in dementia studies is estimated to be between 30 and 40 months from study entry.[8] This study investigates the short-term outcomes of local AD patients from diagnosis over three years, focusing on the longitudinal changes in cognition, BPSD, functional status, and caregiver burden and their placement decisions (in the community or for institutionalisation). We

hypothesize that the majority of AD patients in Singapore are relatively stable, and those who are eventually institutionalised constitute only a minority.

METHODS

This was a longitudinal study which retrospectively reviewed patients who presented to the Dementia Clinic of National Neuroscience Institute, Singapore General Hospital between 2014 and 2016. Patients who fulfilled the diagnostic criteria for AD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) were recruited into the study. Patients diagnosed with dementia with Lewy body (DLB) were also recruited for comparison. Patients with other causes of dementia were excluded. Supplementary Fig. 1 shows the inclusion and exclusion criteria for our study cohort. The study was approved by the Institutional Review Board of Singapore General Hospital (2019/2382) and ethics approval was obtained.

Baseline demographic information such as age, gender, race and caregiver relationship to the patient were collected at the first clinic visit. For this study, we selected caregivers who had spent at least nine hours per week caring for the patient for the past 12 months and who were familiar with the patient's daily habits.

Psychopharmacological medication was documented throughout the study period, including cognitive enhancers, antipsychotic medications and mood medications such as antidepressants and mood stabilisers.

Patients were followed up regularly for a minimum of two years up to three years. At each visit, they were subjected to a thorough clinical examination and mini-mental state examination (MMSE) by a senior neurologist. MMSE was administered following the procedure of Folstein et al.[9] MMSE is a well-established cognitive test used to screen and monitor the progression of dementing illnesses such as AD.[10] MMSE scores ranged from 0 to

30, with a lower score indicating a more impaired cognitive ability. A score of less than 24 out of a possible 30 has been shown to detect dementia fairly accurately.[9,11]

Caregivers were interviewed at each visit to assess their stress and fatigue levels, enrolment of patient to daycare services, desire for institutionalising the patient, as well as their observations about abnormalities in the patient's behaviour to ascertain the presence of BPSD. Majority of BPSD evaluated were derived from the Neuropsychiatric Inventory Questionnaire (NPI-Q),[12] a validated self-administered questionnaire to assess neuropsychiatric symptomatology in routine clinical practice. These include euphoria/elation, dysphoria/depression, apathy/indifference, anxiety, night-time behaviour, agitation/aggression, irritability/lability, delusions, motor disturbances, changes in appetite, disinhibition, and hallucinations. Based on NPI-Q, we also assessed other behaviour, namely verbal outbursts and getting lost.

Functional status was assessed by the patient's ability to travel independently, ambulate in the neighbourhood and at home, wheelchair-bound status, bed-bound status and presence of incontinence. Patients' responses were corroborated by their caregivers.

Data was collected using Microsoft Excel and statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA). Univariate analysis was performed using two-tailed unpaired *t*-test for continuous variables, and Pearson's chi-square test (or Fisher's exact test if cell count was less than 5) for categorical variables. A cut-off of $p \leq 0.05$ was considered statistically significant.

RESULTS

In total, 40 patients (30 AD, 10 DLB) were included in the study. The demographic and clinical characteristics of each group of patients are given in Table I. The median age at diagnosis for

AD patients was 77 years, three years higher than that of DLB patients ($p = 0.345$). 73.3% (22/30) of AD patients and 70% (7/10) of DLB patients were female.

All AD and DLB patients were prescribed at least one cognitive enhancer. 26.7% (8/30) AD patients took at least one mood medication, as compared to 50% (5/10) of DLB patients. There was a smaller proportion of patients on antipsychotics in the AD group (16.7%, 5/30) than the DLB group (50%, 5/10). The difference in medications between the two groups was not statistically significant.

Changes in MMSE scores of AD and DLB patients over the three years are reflected in Table II. Most patients had moderate dementia at diagnosis (MMSE 13–20),[9] with a mean MMSE of 17.8 in the AD group and 18.2 in the DLB group. DLB patients had higher MMSE scores than AD patients during the first two years of follow-up, but the latter group achieved a higher mean MMSE score after three years. However, these differences were not statistically significant.

Changes in neuropsychiatric symptoms over the three years are presented in Table II. During the first visit, within the DLB group, 40% (4/10) experienced anxiety ($p < 0.01$) and 50% (5/10) had hallucinations ($p < 0.01$), while neither symptom was experienced in AD patients. 70% (7/10) of DLB patients demonstrated night-time behaviour, compared to 10% (3/10) of AD patients ($p < 0.01$). After three years of follow-up, the incidence of anxiety, hallucinations and night-time behaviour in DLB patients decreased to 0%, 12.5% (1/8) and 12.5% (1/8), respectively.

At two years, 20% (2/10) of DLB patients showed apathy ($p = 0.012$), in contrast to none from the AD patients. This difference was also seen at three years: 50% (4/8) of patients from the DLB group displayed apathy as compared to 4.55% (1/22) of AD patients ($p = 0.003$).

Through all three years, hallucinations was the only symptom present consistently among DLB patients, while delusions and irritability were encountered consistently among AD patients.

Changes in functional status, caregiver stress and nursing home status of patients over the three years are reflected in Table III. At baseline, 80% (24/30) of AD patients could travel independently as compared to 70% (7/10) of DLB patients. This trend continued through the first and second years, with 60% (18/30) of AD patients but only 30% (3/10) of DLB patients having independent travel in the first year ($p = 0.046$), then 66.7% (20/30) and 20% (2/10) respectively, in the second year ($p = 0.010$).

A greater percentage of AD patients were able to ambulate independently at home as compared to DLB patients (Year 1: 90% (27/30) vs. 80% (8/10), $p = 0.017$; Year 2: 90% (27/30) vs. 60% (6/10), $p = 0.031$). This was also seen after three years. Furthermore, AD patients were more ambulant in their neighbourhood compared to DLB patients for all three years (Year 1: 76.6% (23/30) vs. 40% (4/10), $p = 0.006$; Year 2: 76.6% (23/30) vs. 20% (2/10), $p = 0.001$; Year 3: 77.2% (17/22) vs. 12.5% (1/8), $p = 0.001$).

A greater proportion of DLB patients were incontinent as compared to AD patients. This trend occurred consistently throughout all three years (Year 1: 20% (2/10) vs. 0% (0/30), $p = 0.017$; Year 2: 60% (6/10) vs. 16.6% (5/30), $p = 0.008$; Year 3: 75% (6/8) vs. 22.7%(5/22), $p = 0.009$).

As evident, functional status across both groups declined over the course of the study, but in general, AD patients retained greater functional ability than their DLB counterparts.

Majority of caregivers reported overall stable function of the patient during the first clinic visits – AD group: 86.7% (26/30); DLB group: 90% (9/10). After three years, only 3 (7.5%) patients were institutionalised, including 2 AD patients and 1 DLB patient. 72.7% (16/22) of caregivers reported overall stable function of AD patients, with only 4.55% (1/22)

expressing stress or fatigue. 27.2% (6/22) and 12.5% (1/8) in the AD group and DLB group, respectively, were put in adult daycare after three years.

DISCUSSION

Our results indicate that despite BPSD in some patients, AD patients in Singapore are stable at short-term, with relatively preserved function, more so than DLB patients. The rate of institutionalisation is also surprisingly low (7.5%), much lower than that in France (11.84%, over 2 years)[13] and in Canada (50.9%, over 5 years).[14] This could be due to a number of reasons. Firstly, functional status of AD patients in our cohort was generally stable in the short-term, with 90% (27/30) ambulant at home and 66.7% (20/30) still able to travel independently at 2 years from diagnosis. It is well established that severity of functional impairment is an independent predictor for caregivers' decision to institutionalise a PWD.[7] Moreover, only 22.7% (5/22) of AD patients in our study were incontinent at three years. Since incontinence increases the likelihood of institutionalisation,[7] having such a low rate of incontinence among our AD population is likely associated with a lower rate of institutionalisation. Furthermore, majority of caregivers expressed overall stable function of AD patients with only a small percentage (4.55%, 1/22) reporting stress or fatigue after three years. Caregiver stress is directly related to caregiver burden.[15] Thus, a low caregiver burden along with the relatively preserved function of AD patients in Singapore may contribute to the low rates of institutionalisation.

Secondly, caregivers in Singapore may prefer caring for a relative with dementia in their own homes rather than placing them in nursing homes, which could reflect intrinsic Asian values in our society, such as filial piety and duty, as suggested by Tew et al.[16] This could possibly be another reason for the low rates of institutionalisation seen in our cohort. Caregiver gain is a protective factor and is correlated with the decision to continue caring for the patient

at home.[16] Further studies should investigate the specific gains in dementia caregiving from a Singaporean perspective and if these gains could predict a delay in institutionalisation.

Loss of independent function appears to occur earlier in DLB as compared to AD, in line with existing literature[17] that functional decline in DLB is more rapid than that seen in AD.

With regard to BPSD, a smaller proportion of patients in the AD group had anxiety, night-time behaviour and hallucinations as compared to the DLB group at baseline, and apathy was less often reported during follow-up in the AD group. This is congruent with existing literature that psychiatric features are more likely to be present in early stages of DLB when compared to AD.[18] In particular, hallucinations, night-time behaviour and apathy were more commonly seen in DLB patients than AD patients.[19] Of note, there was a higher prevalence of BPSD symptoms among DLB patients in the first year of diagnosis as compared to the subsequent years. We hypothesised that this could be due to the early commencement of medications from time of diagnosis and the adoption of non-pharmacological interventions. Firstly, 80% (8/10) of the DLB patients were started on cognitive enhancers at the first visit. By the second visit, all patients were on rivastigmine, while 30% (3/10) and 40% (4/10) of patients were taking fluvoxamine and quetiapine, respectively. Rivastigmine has demonstrated behavioural benefits in DLB patients,[20] and quetiapine has been found to be effective in managing BPSD.[21] In addition, caregivers learning positive coping strategies to manage behavioural symptoms of DLB patients could also contribute to the improvement in BPSD reported by caregivers.

Hart et al found that motor disturbances, aggression, appetite changes and sleep disturbances played a bigger role in causing caregiver stress than psychological symptoms did.[22] In our cohort, only a small percentage of AD patients displayed these behavioural changes throughout the three years, potentially leading to lower levels of caregiver distress.

Furthermore, physical aggression and depressive symptoms, two main predictors of institutionalisation,[23] were reported in very few patients in our AD group, which could explain the low incidence of institutionalisation seen in our study.

Finally, we noted that for both groups, using community daycare services was uncommon. The low uptake of daycare services by both groups of patients could be due to the the low incidence of neuropsychiatric symptoms, functional impairment and caregiver stress seen in our study, and thus daycare enrolment may not be warranted for these patients. Nonetheless, given that some studies[24] have already demonstrated the effectiveness of dementia daycare services in delaying institutionalisation, it would be prudent to increase efforts in promoting early enrolment.

The present study has some limitations. This was a retrospective study with a small sample size of patients. Generalisation of our results to the larger community must thus be done cautiously. Furthermore, some of the observations at Year 3 of follow-up may have been affected by dropouts from the study. Most of our AD patients had a modest mean MMSE score at diagnosis. Given the retrospective nature of this study, patients with higher initial MMSE scores could have been sampled, which could have affected our results, as the rate of institutionalisation is influenced by AD severity at baseline with more severe patients having a higher risk of being institutionalised.[13] Moreover, the length of follow-up may not be adequate to observe the deterioration in dementia patients given that our study population consisted of dementia patients who had a low incidence of behavioural issues and functional disability. With regard to the study methodology, we did not employ existing established questionnaires such as the Zarit Burden Interview to ascertain caregiver stress. Instead, the variable ‘expression of stress/fatigue’ was modelled after question 3 of the abbreviated Zarit Burden Interview.[25] In addition, the variable ‘overall stable function’ was determined by caregivers subjectively reporting their overall perception of the function of the patient at each

follow-up. A larger scale study would be useful to validate these variables in evaluating the patient's overall progress in a longitudinal manner from the caregiver's point-of-view. Finally, our sample population consisted almost entirely of Chinese subjects. Singapore has a multiracial society and sociocultural factors are important determinants of outcomes associated with dementia care. Thus, this study's findings may not be directly applicable to that of other ethnic groups in Singapore.

In conclusion, majority of patients with AD in Singapore are stable at short-term (within three years of diagnosis), with minimal caregiver burden and low rates of institutionalisation. Providing support for caregivers through community care services deserves careful consideration as a means to keep their caregiver burden low and to delay their decision for institutionalisation.

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Table I: Patient and caregiver demographics

	Number (%)		
	Alzheimer's Disease (AD) n=30	**Dementia with Lewy Body (DLB) n=10**	**p-value**
Patient characteristics			
Age at presentation, years, median [IQR]	79 [74-84]	73 [69-78]	0.345
Gender			
Female	22 (73.3)	7 (70)	0.838
Male	82 (26.7)	3 (30)	
Race			
Chinese	29 (96.7)	10 (100)	0.559
Malay	0	0	
Indian	0	0	
Others	1 (3.33)	0	
Medications (at Year 2 of follow-up)			
Cognitive enhancers	30 (100)	10 (100)	NA
Antipsychotics	5 (16.7)	5 (50)	0.087
Mood medications	8 (26.7)	5 (50)	0.195
Main caregiver characteristics			
Spouse	11 (36.7)	2 (20)	0.375
Children	17 (56.7)	8 (80)	
Maid	2 (6.67)	0	

Table II: MMSE scores and behavior over 3 years of follow-up

	Baseline Number(%)			**Year 1**			**Year 2**			**Year 3**		
	AD n=30	DLB n=10	P	AD n=30	DLB n=10	P	AD n=30	DLB n=10	P	AD n=22*	DLB n=8*	P
MMSE scores, mean (±s.d.)	17.8 (6.39)	18.2 (5.35)	0.901	16.2 (6.61)	17.0 (4.96)	0.822	16.9 (5.19)	17.0 (4.96)	0.988	15.8 (5.20)	13.7 (5.67)	0.471
Neuropsychiatric symptoms												
Euphoria/Elation	1 (3.3)	1 (10)	0.402	0	0	NA	0	0	NA	0	0	NA
Depression/Dysphoria	1 (3.3)	1 (10)	0.402	2 (6.67)	0	0.376	0	0	NA	0	0	NA
Apathy/Indifference	6 (20)	2 (20)	1.0	2 (6.67)	0	0.376	0	2 (20)	**0.012**	1 (4.55)	4 (50)	**0.003**
Anxiety	0	4 (40)	**< 0.01**	0	0	NA	0	0	NA	0	0	NA
Nighttime Behavior	3 (10)	7 (70)	< 0.01	1 (3.3)	2 (20)	0.107	0	0	NA	1 (4.55)	1 (12.5)	0.440
Agitation/Aggression	1 (3.3)	1 (10)	0.402	0	0	NA	1 (3.3)	3 (30)	**0.015**	1 (4.55)	0	0.540
Irritability/Lability	1 (3.3)	4 (40)	0.783	2 (6.67)	1 (10)	0.798	2 (6.67)	1 (10)	1	1 (4.55)	0	0.540
Verbal Outbursts	2 (6.67)	0	0.402	0	1 (10)	0.096	0	0	NA	0	0	NA
Hallucinations	0	5 (50)	**< 0.01**	1 (3.3)	1 (10)	0.452	2 (6.67)	1 (10)	0.729	3 (13.6)	1 (12.5)	0.935
Delusions	6 (20)	4 (40)	0.206	1 (3.3)	0	0.537	2 (6.67)	1 (10)	0.729	2 (9.09)	0	0.377
Aberrant Motor	0	1 (10)	0.079	1 (3.3)	0	0.537	1 (3.3)	0	0.559	1 (4.55)	0	0.540
Appetite/Eating	0	0	NA	0	0	NA	0	0	NA	0	0	NA
Disinhibition	0	0	NA	0	0	NA	0	0	NA	0	0	NA
Getting lost	2 (6.67)	2 (20)	0.224	0	0	NA	0	1 (10)	0.559	0	1 (12.5)	0.540

**10 patients were lost-to-follow-up at the 3rd year of follow-up; AD: Alzheimer's dementia; DLB: Dementia with Lewy Body*

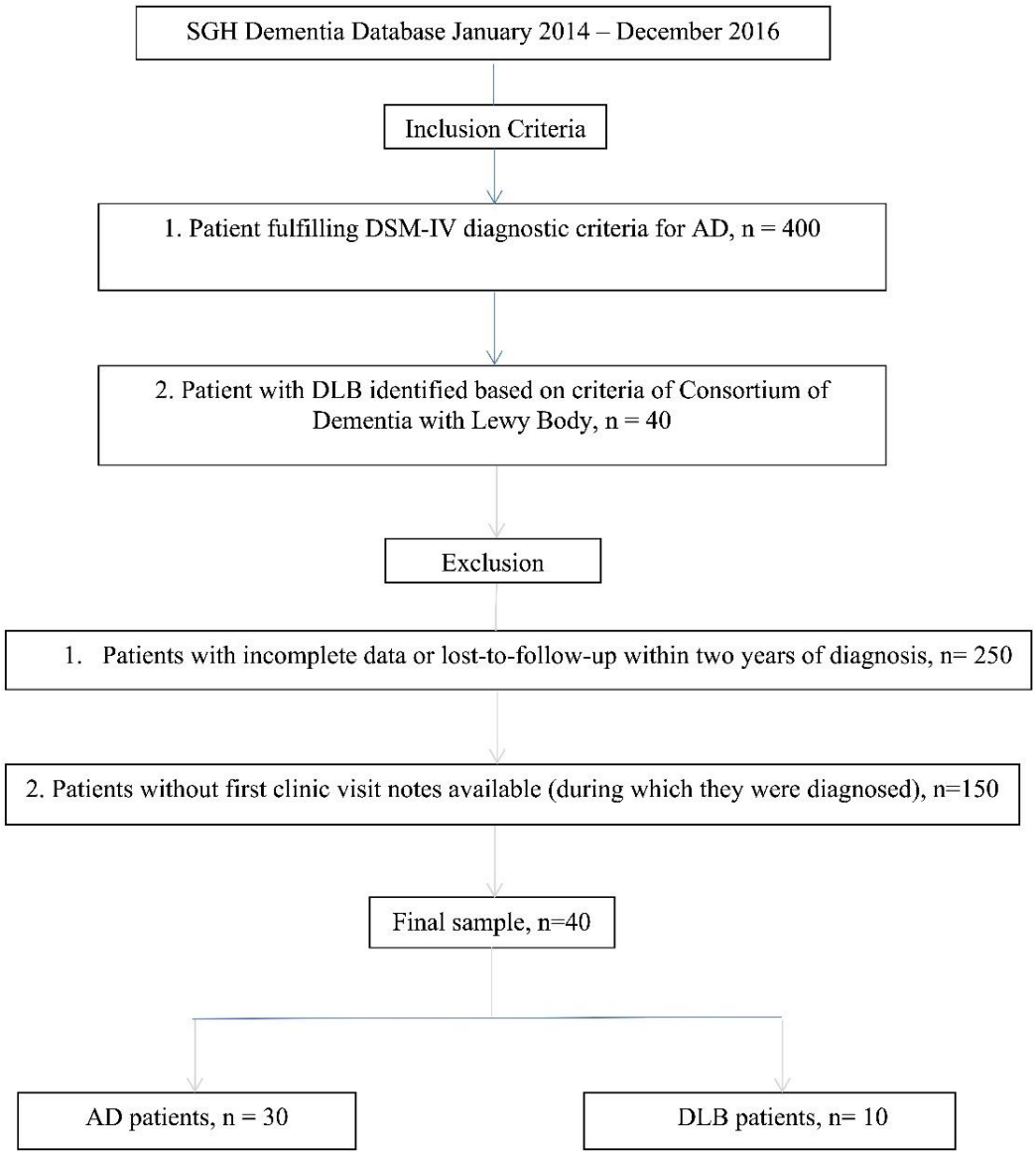
Table III: Functional status and caregiver stress over 3 years of follow-up

	Year 0 Number(%)			**Year 1**			**Year 2**			**Year 3**		
	AD n=30	DLB n=10	P	AD n=30	DLB n=10	P	AD n=30	DLB n=10	P	AD n=22*	DLB n=8*	p
Functional status												
Independent travel	24 (80)	7 (70)	0.512	18 (60)	3 (30)	**0.046**	20 (66.7)	2 (20)	**0.010**	11 (50)	1 (12.5)	0.064
Ambulant at home	30 (100)	10 (100)	NA	27 (90)	8 (80)	**0.017**	27 (90)	6 (60)	**0.031**	20 (90.9)	5 (62.5)	0.065
Ambulant in neighborhood	26 (86.6)	7 (70)	0.230	23 (76.6)	4 (40)	**0.006**	23 (76.6)	2 (20)	**0.001**	17 (77.2)	1 (12.5)	**0.001**
Wheelchair-bound	0	0	NA	0	0	NA	2 (6.67)	0	0.402	1 (4.55)^	1 (12.5)	0.440
Bed-bound	0	0	NA	0	0	NA	1 (3.33)	0	0.559	1 (4.55)	1 (12.5)	0.440
Incontinent/on diapers	0	1 (10)	0.079	0	2 (20)	**0.017**	5 (16.6)	6 (60)	**0.008**	5 (22.7)	6 (75.0)	**0.009**
Caregiver status												
Overall stable function	26 (86.7)	9 (90)	0.783	22 (73.3)	8 (80)	0.919	23 (76.6)	5 (50)	0.111	16 (72.7)	5 (62.5)	0.589
Expression of stress/fatigue	1 (3.33)	2 (20)	0.083	2 (6.67)	0	0.224	2 (6.67)	2 (20)	0.542	1 (4.55)	0	0.540
Patient placement												
Patient in daycare	0	0	NA	1 (3.33)	1 (10)	0.452	2 (6.67)	0	0.402	6 (27.2)	1 (12.5)	0.398
Patient in nursing home	0	0	NA	1 (3.33)	0	0.537	2 (6.67)	1 (10)	0.729	2 (9.09)	1 (10)	0.783

^1 patient who was wheelchair bound in Year 2 was subsequently lost-to-follow-up in Year 3 AD: Alzheimer's dementia; DLB: Dementia with Lewy Body

APPENDIX

Supplementary Fig. 1 Flowchart of study cohort selection



SGH: Singapore General Hospital; DSM-IV: Diagnostic and Statistical Manual Of Mental Disorders, 4th edition; AD: Alzheimer's Dementia; DLB: Dementia with Lewy Body