

Psychometric Properties of Alzheimer's Disease Assessment Scale-Cognitive Subscale for Mild Cognitive Impairment and Mild Alzheimer's Disease Patients in an Asian Context

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Abstract

Introduction: The purpose of the current study is to assess the psychometric properties of Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) on patients with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) in a multicultural Asian context. **Materials and Methods:** Sixty-four mild AD patients (mean age $\pm$ SD; 72.24 ± 7.88 years), 80 MCI patients (66.44 ± 7.45 years) and 125 healthy controls (HCs) (61.81 ± 6.96 years) participated in the study. Participants underwent a clinical interview and serial neuropsychological testing. ADAS-Cog total and subtest scores were compared across the 3 groups. Receiver operating characteristics (ROC) analysis were performed and sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated. **Results:** Patients with MCI attained significantly worse neuropsychological test scores than healthy controls but significantly better results than patients with mild AD on ADAS-Cog total score, subtest items, and the delayed recall item ($P < 0.001$). The best cutoff score to differentiate between MCI and HC was ≥ 4 (sensitivity = 0.73, specificity = 0.69, PPV = 0.90, NPV = 0.40), while the best cutoff score to distinguish between MCI and mild AD was ≥ 12 (sensitivity = 0.86, specificity = 0.89, PPV = 0.99, NPV = 0.32). Evidence of internal consistency of the ADAS-Cog (Cronbach $\alpha = 0.85$) as well as convergent validity with the Mini-Mental State Examination (MMSE) ($\rho = -0.75$) and Montreal Cognitive Assessment (MoCA) ($\rho = -0.81$) (both $P < 0.001$) was also found. **Conclusion:** The ADAS-Cog which is widely used in clinical trials is applicable to the Asian cohort. It is useful in the detection of MCI and mild AD as well as in distinguishing these 2 conditions.

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Introduction

The Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) is widely used in research settings to detect and follow-up cognitive deficits in persons suffering from Alzheimer's disease (AD), a neurodegenerative disorder associated with progressive, gradual decline in memory and cognition.¹ The ADAS-Cog is a psychometrically reliable and valid tool^{1,2} that is commonly adopted as both a process and outcome measure in multinational AD pharmacological treatment trials and used in a plethora of settings including but not limited to the assessment of day-to-day functional status,^{3,4} disease staging⁵ and caregiver burden.⁶ Although not equivalent

to a comprehensive neuropsychological test battery, it provides a more complete assessment in comparison to other cognitive screening instruments.⁷

The extensive usage of the ADAS-Cog is reflected by several psychometric validation studies in diverse cultures and languages (e.g. Turkish version,⁸ Slovak version,⁹ Hong Kong version,¹⁰ Brazil version¹¹). Slight modifications were made to the original English version in an attempt to make the ADAS-Cog more culturally nuanced. For instance, the word 'ocean' in the word recall task was replaced by 'sea' because the latter word reflected higher imagery to Turkish people.¹²

ADAS-Cog 11 scale (total score ranges from 0 to 70)

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comprises 11 items measuring cognition: 3 trials of an immediate recall task comprising a 10-word list (average score), comprehension of commands, constructional praxis, object and finger naming, ideational praxis, orientation, 1 trial of a 12-word recognition task, word-finding difficulty, expressive language, language comprehension and recall of instructions. The ADAS-Cog 12 scale includes an additional 10-word delayed recall list administered 5 minutes after the immediate recall task (total score ranges from 0 to 80).¹² Impairment in these functions forms the constellation of core and peripheral cognitive symptoms in AD. Higher scores denote greater impairment and errors made by either commission or omission. In recent years, however, more attention has been paid to mild cognitive impairment (MCI), generally defined as a prodromal condition for AD¹³ with an annual progression rate of 10% to 15% to dementia in tertiary referral clinic settings.¹⁴

A few studies have examined the clinical utility of the ADAS-Cog in predicting the conversion from MCI to dementia with proposed cutoff scores.^{15–17} A baseline cutoff score of 9.5 on ADAS-Cog predicted good conversion rate (area under the curve (AUC) = 0.67; sensitivity value = 0.62; specificity value = 0.73) from amnesic MCI to AD 1 year later.¹⁵ ADAS-Cog has also been demonstrated to be a promising tool to detect patients with MCI, using a cutoff score of 6 on total ADAS-Cog (sensitivity value = 0.73 and specificity value = 0.89).¹⁶ The normative cutoff score on ADAS-Cog has also been determined to be ≥ 5 and the best ADAS-Cog cutoff score for dementia is ≥ 12 (AUC = 0.94; sensitivity value = 0.89; specificity value = 0.89).¹⁸

The normative data and cutoff scores of the ADAS-Cog derived from the sample characteristics of the above-mentioned studies, however, may not be representative of and generalisable to the sociodemographic realities in the Asian context.^{19–21} In particular, there remains a knowledge gap with regards to the ADAS-Cog as a culturally appropriate and psychometrically valid tool in multicultural societies such as Singapore. For example, Monllau and colleagues (2007) determined the cutoff score for MCI based on a patient group with an average formal education of 13 years to be 5 based on normal subjects who had 10 to 21 years of education. These highly educated groups may not be reflective of the lower education level attained by the normal elderly in Singapore. Based on the Census of Population report in 2010, 65.6% of the elderly aged 55 years and above obtained less than 10 years of formal education.¹⁹ A recent publication from the Singapore Longitudinal Ageing Study (SLAS) which enrolled healthy elderly Chinese from the local community highlighted the need for neuropsychological batteries to be tailored to less well-educated Asian elderly.^{21,22}

The purpose of the current study is to therefore extend

our understanding of the psychometric properties of the ADAS-Cog in the Asian context. We assessed the clinical utility of the ADAS-Cog to detect patients with MCI and mild AD in Singapore. We determined the optimal cutoff scores (including AUC, sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]), internal consistency, and convergent validity of the ADAS-Cog with other global cognition measures.

Materials and Methods

Power Analysis

Based on an a priori power analysis, it was determined that a sample size of at least 72 participants was required to observe a medium between-groups effect size (Cohen's $f = 0.30$) with a level of 0.05 and power of 0.80.²³

Procedures

A total of 269 subjects, aged 50 years and above, were enrolled between 2010 and 2014 in this cross-sectional study. Patients attending a tertiary neurology institute based in Singapore who either fulfilled Petersen's criteria for MCI²⁴ or the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD²⁵ were invited for the study. Patients who fulfilled Petersen's criteria of MCI were also required to have a Clinical Dementia Rating (CDR) sum of boxes (SOB) score of 0.5 and patients meeting NINCDS-ADRDA criteria for AD were required to have CDR of 0.5 to 1 to ensure that only patients with mild AD were recruited.^{26,27} Healthy controls were recruited from the community and were required to have a CDR of 0. Participants were excluded if they had major depression and serious systemic or metabolic abnormalities that could contribute to the cognitive deficits. The eligible participants underwent a battery of neuropsychological tests that included the ADAS-Cog. Locally-validated versions of the Mini-Mental State Examination (MMSE)^{28,29} and Montreal Cognitive Assessment (MoCA)^{30,31} were administered as global cognition measures and the Frontal Assessment Battery (FAB) was used to assess executive dysfunction.^{32,33} All the tests were administered in either English or Mandarin by 3 experienced raters (NHZ, EE, and LL). The raters were experienced psychologists who have and were blinded to the clinical information. The Mandarin version of the tests was forward and backward translated by native bilinguals proficient in both languages and was locally validated by prior studies.^{29,31,33} All raters assessed the MMSE, MOCA, ADAS-Cog, and FAB independently and were blinded to the clinical data. Inter-rater agreement for the ADAS-Cog among the 3 raters was excellent ($\kappa = 0.86 - 1$; mean = 0.99;

median = 1.00). Ethics approval was obtained from the SingHealth Centralised Institutional Review Board (CIRB). All participants provided voluntary informed consent.

ADAS-Cog Measures

The total and subtest scores on the ADAS-Cog were compared across the 3 diagnostic groups. Higher total score in ADAS-Cog reflects greater degree of cognitive deficit (scale range 0–70). The ADAS-Cog comprises 11 items and was administered according to the methodology described by Rosen and colleagues:

1. Word recall task (3 trials of immediate recall task of 10 high imagery words) (scale range = 0–10)
2. Commands (understand and carry out 1 to 5 steps commands) (scale range = 0–5)
3. Constructional praxis (duplication of 4 different geometric shapes) (scale range = 0–5)
4. Naming (naming of fingers and 4 low frequency, 4 medium frequency and 4 high frequency objects) (scale range = 0–5)
5. Ideational praxis (performing a familiar yet complex sequenced task) (scale range = 0–5)

Table 1. Mean, Standard Deviations and Median Scores across the 3 Diagnostic Groups on Key Sociodemographic, Clinical, and Cognitive Variables

	HCs (n = 125) M ± SD (Median)	MCI (n = 80) M ± SD (Median)	Mild AD (n = 64) M ± SD (Median)	Overall P Value
Age (years)	61.81 ± 6.96 (61)	66.44 ± 7.45 (67.01)	72.24 ± 7.88 (73.42)	<0.001
Education (years)	11.70 ± 3.13 (10)	10.88 ± 3.89 (10)	6.02 ± 5.21 (4)	<0.001
Gender, n (%)				
Males	39 (31.2%)	40 (50%)	40 (62.5%)	<0.001
Females	86 (68.8%)	40 (50%)	24 (37.5%)	
Race, n (%)				
Chinese	113 (90.4%)	71 (88.75%)	49 (76.56%)	0.024
Malay, Indian, Eurasian and Others	12 (9.6%)	9 (11.25%)	15 (23.44%)	
CDR-SOB (scale range 0 – 2)	0.08 ± 0.18 (0)	0.45 ± 0.20 (0.5)	1.00 ± 0.42 (1)	<0.001
GDS (scale range 0 – 15)	2.03 ± 2.58 (1)	2.12 ± 1.95 (2)	2.56 ± 2.46 (2)	0.049
MMSE (scale range 0 – 30)	29.13 ± 1.05 (29)	27.38 ± 2.11 (27)	22.32 ± 4.80 (23)	<0.001
MoCA (scale range 0 – 30)	28.41 ± 1.81 (29)	25.47 ± 3.65 (26)	19.22 ± 5.92 (20.5)	<0.001
FAB (scale range 0 – 18)	17.47 ± 0.76 (18)	15.92 ± 2.26 (17)	13.50 ± 4.13 (14.50)	<0.001
ADAS-Cog				
11-item total score	3.99 ± 2.68 (3)	8.63 ± 5.43 (7)	20.88 ± 10.07 (19)	<0.001
12-item total error	5.26 ± 3.73 (4)	11.76 ± 7.21 (10.5)	28.39 ± 11.89 (27)	<0.001
Memory				
Word recall	2.14 ± 1.19 (2)	3.28 ± 1.52 (3)	6.06 ± 2.04 (6)	<0.001
Word recognition	0.87 ± 1.30 (0)	1.66 ± 1.95 (1)	5.39 ± 3.59 (5)	<0.001
Remembering instructions	0.10 ± 0.32 (0)	0.40 ± 0.69 (0)	1.39 ± 1.47 (1)	<0.001
Orientation	0.04 ± 0.20 (0)	0.25 ± 0.46 (0)	2.16 ± 2.15 (1.5)	<0.001
Language				
Naming (fingers and objects)	0.37 ± 0.58 (0)	0.60 ± 0.74 (0)	1.08 ± 1.03 (1)	<0.001
Word-finding difficulty	0.10 ± 0.31 (0)	0.41 ± 0.72 (0)	0.84 ± 0.98 (1)	<0.001
Following oral commands	0.21 ± 0.48 (0)	0.66 ± 0.99 (0)	1.14 ± 1.13 (1)	<0.001
Expressive language	0.02 ± 0.15 (0)	0.23 ± 0.55 (0)	0.67 ± 0.91 (0)	<0.001
Comprehension	0.05 ± 0.22 (0)	0.51 ± 0.68 (0)	1.05 ± 0.99 (1)	<0.001
Praxis				
Constructional praxis	0.09 ± 0.28 (0)	0.56 ± 1.04 (0)	0.66 ± 0.70 (1)	<0.001
Ideational praxis	0.02 ± 0.13 (0)	0.06 ± 0.24 (0)	0.42 ± 0.75 (0)	<0.001
Delayed recall	1.26 ± 1.53 (1)	3.14 ± 2.42 (3)	7.52 ± 2.93 (9)	<0.001

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SOB: Clinical Dementia Rating-Sum of Boxes score; GDS: Geriatric Depression Scale; HC: Healthy control; MCI: Mild cognitive impairment, SD: Standard deviation

6. Orientation (assessment of temporal and geographic orientation) (scale range = 0-8)
7. Word recognition (discriminating words that had been presented from distractors) (scale range = 0-12)
8. Remembering instructions (of preceding recognition task) (scale range = 0-5)
9. Spoken language ability (assessment of patient's ability to communicate) (scale range = 0-5)
10. Word-finding difficulty (assessment of patient's ability to express himself with precise words) (scale range = 0-5)
11. Language comprehension (assessment of patient's ability to understand speech) (scale range = 0-5)

Items 1 to 7 were performance-based while items 8 to 11 were rater-based. The ADAS-Cog delayed recall item was administered in between Constructional Praxis and Naming subtest to prevent interference from the naming list. A 90-second time limit was given for the 10-word immediate and delayed recall (scale range = 0-10).

Data Analysis

The statistical analyses were conducted using SPSS (Statistical Package for Social Sciences, Version 20.0). Continuous scores which were not normally distributed as reflected by the Shapiro-Wilk tests ($P < 0.05$) were analysed using non-parametric methods: the omnibus Kruskal-Wallis H test, a non-parametric equivalent of the one-way ANOVA test,³⁴ was used to compare statistical differences among the 3 groups, and non-parametric Mann-Whitney U test for between-groups comparisons. Age which was normally distributed was analysed using parametric methods: one-way analysis of variance (ANOVA) across groups and independent sample t-test was used for between-groups comparisons. Dichotomous variables such as gender (0 = male; 1 = female) were analysed using the χ^2 test. All statistical tests for significances were two-tailed at a probability level of 0.05. The best ADAS-Cog cutoff scores, defined as maximal sensitivity and specificity³⁵ to differentiate between MCI and HC as well as MCI and mild AD were determined using receiver operating characteristic (ROC) analysis.³⁶ Cohen's kappa was calculated to examine inter-rater agreement among the 3 trained raters (NHZ, EE, and LL) for a random sample of 30% of the tests.³⁷ The AUC, sensitivity, specificity, PPV, and NPV were also calculated for ADAS-Cog 11-item and 12-item scales, as well as a composite ADAS-Cog Episodic Memory subscale. Spearman's rank correlation coefficient was used to examine the convergent validity of ADAS-Cog with MMSE and MoCA.

Results

Participants

We compared 64 mild AD patients, 80 MCI patients and 125 HCs in terms of key sociodemographic, clinical, and cognitive variables (Tables 1 and 2). Age showed significant correlations with ADAS-Cog total score for both the 11-item (Pearson's $r = 0.42$, $P < 0.001$) and 12-item ($r = 0.45$, $P < 0.001$) scales. The effect remained when divided into age strata ($F(2, 148) = 36.44$, $P < 0.001$). The mean age in years ($\pm$ SD) for the HCs, MCIs and mild ADs were 61.81 ± 6.96 , 66.44 ± 7.45 and 72.24 ± 7.88 , respectively.

Table 2. *P* Values of Demographics and Cognitive Scores in Between-Groups Comparisons

	HC vs MCI	MCI vs Mild AD	HC vs Mild AD
Age (years)	0.00002	0.00006	0.00001
Education (years)	0.20162	0.00001	0.00001
Gender	0.00698	0.13361	0.00004
Race	0.70391	0.05118	0.01009
CDR-SOB	0.00001	0.00001	0.00001
GDS	0.15604	0.28654	0.01714
MMSE	0.00001	0.00001	0.00001
MoCA	0.00001	0.00001	0.00001
FAB	0.00001	0.00002	0.00001
ADAS-Cog			
11-item total error score	0.00001	0.00001	0.00001
12-item total error score	0.00001	0.00001	0.00001
Memory			
Word recall	0.00001	0.00001	0.00001
Word recognition	0.00178	0.00001	0.00001
Remembering instructions	0.00006	0.00001	0.00001
Orientation	0.00002	0.00001	0.00001
Language			
Naming objects/figures	0.02155	0.00434	0.00001
Word-finding difficulty	0.00037	0.00199	0.00001
Commands	0.00011	0.00354	0.00001
Language	0.00028	0.00018	0.00001
Comprehension	0.00001	0.00073	0.00001
Praxis			
Constructional praxis	0.00001	0.04625	0.00001
Ideational praxis	0.07443	0.00025	0.00001
Delayed recall	0.00001	0.00001	0.00001

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SOB: Clinical Dementia Rating Sum of Boxes score; FAB: Frontal Assessment Battery; MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale

There were also overall significant differences in education ($H(2) = 46.76$, $P < 0.00001$), gender ($\chi^2(2) = 18.34$, $P = 0.001$) and race ($\chi^2(2) = 7.74$, $P = 0.024$). The healthy controls were similar in education level to the MCI patients (11.70 ± 3.13 vs 10.88 ± 3.89 ; $U = 4377.00$, $P = 0.20162$), but had significantly higher education compared to mild AD patients (11.70 ± 3.13 vs 6.02 ± 5.21 ; $U = 1236.50$, $P = 0.00001$). MCI patients in turn received longer years of formal education than mild AD patients (10.88 ± 3.89 vs 6.02 ± 5.21 ; $U = 1236.00$, $P = 0.00001$). The gender distribution was relatively similar between the MCI and mild AD group (percentage of males: 50.00 vs 62.50; $\chi^2(1) = 2.25$, $P = 0.13361$), but the ratio of males to females were lower when comparing HCs versus MCI (31.20 vs 50.00; $\chi^2(1) = 7.28$, $P = 0.00698$) and HC versus mild AD ($\chi^2(1) = 17.05$, $P = 0.00004$) patients. The race distribution was different between the mild AD and HCs wherein a higher proportion of non-Chinese were present in the former group ($\chi^2(1) = 6.62$, $P = 0.01$).

Functional status as measured by the CDR was also associated with ADAS-Cog 11-item ($r = 0.67$, $P < 0.001$) and 12-item ($r = 0.68$, $P < 0.001$) scales. The positive associations are illustrated by the boxplots in Figures 1a and 1b. On the other hand, depression as reflected by the Geriatric Depression Scale (GDS) correlated neither with the ADAS-Cog 11-item ($r = 0.09$, $P = 0.152$) nor the 12-item ($r = 0.10$, $P = 0.113$) total error scales.

Cognitive Scores

The total scores and individual subtest scores of ADAS-

Cog were significantly different among the 3 diagnostic groups ($H(2) = 143.21$, $P < 0.001$). The ADAS-Cog subtest scores of healthy controls were significantly different from MCI patients except on the ideational praxis subtest (0.02 ± 0.13 vs 0.23 ± 0.55 ; $U = 4767.50$, $P = 0.07443$). The ADAS-Cog scores of MCI patients were significantly different from mild AD patients on all subtests (all $P < 0.05$).

ADAS-Cog 11-item and 12-item Cutoff Scores

The best cutoff score to differentiate MCI and HC was ≥ 4 (AUC = 0.78 [95% confidence interval (CI), 0.71 to 0.84]; sensitivity = 0.73, specificity = 0.69, PPV = 0.90, NPV = 0.40), while the best cutoff score to distinguish between MCI and mild AD was ≥ 12 (AUC = 0.93 [95% CI, 0.80 to 0.95]; sensitivity = 0.86, specificity = 0.89, PPV = 0.99, NPV = 0.32). When the ADAS-Cog delayed recall subtest was added, the optimal cutoff score for ADAS-Cog 12-item scale to differentiate between MCI and HCs was ≥ 5 (AUC = 0.79 [95% CI, 0.72 to 0.85]; sensitivity = 0.90, specificity = 0.53, PPV = 0.88, NPV = 0.58), ≥ 21 to discriminate between MCI and mild AD (AUC = 0.88 [95% CI, 0.82 to 0.94]; sensitivity = 0.79, specificity = 0.89, PPV = 0.98, NPV = 0.37) and ≥ 21 to differentiate between HC and mild AD (AUC = 0.98 [95% CI, 0.96 to 0.99]; sensitivity = 0.73, specificity = 1.00, PPV = 0.88, NPV = 1.00). Adjusting for age and education did not improve AUC, sensitivity and specificity values for both ADAS-Cog 11-item and 12-item scales (see Table 3 for a summary as well as Figures 2 and 3 for ROC curves).

Table 3. Cutoff Scores of ADAS-Cog Measures and Associated Sensitivity, Specificity, PPV and NPV

	Cutoff	AUC	95% CI	Sensitivity	Specificity	PPV	NPV
ADAS-Cog 11 (scale range = 0 – 70)							
MCI vs HC (n = 205)	≥ 4	0.78	0.71 – 0.84	0.73	0.69	0.81	0.61
MCI vs mild AD (n = 145)	≥ 12	0.93	0.80 – 0.95	0.86	0.89	0.87	0.74
HC vs mild AD (n = 189)	≥ 14	0.97	0.94 – 0.99	0.81	1.00	0.91	1.00
ADAS-Cog 12 (scale range = 0 – 80)							
MCI vs HC (n = 205)	≥ 5	0.79	0.72 – 0.85	0.90	0.53	0.88	0.58
MCI vs mild AD (n = 145)	≥ 21	0.88	0.82 – 0.94	0.79	0.89	0.98	0.37
HC vs mild AD (n = 189)	≥ 21	0.98	0.96 – 0.99	0.73	1.00	0.88	1.00
ADAS-Cog Episodic Memory Composite Scale* (scale range = 0 – 32)							
MCI vs HC (n = 205)	≥ 6	0.73	0.66 – 0.80	0.61	0.73	0.86	0.41
MCI vs mild AD (n = 145)	≥ 14	0.87	0.81 – 0.93	0.76	0.85	0.97	0.35
HC vs mild AD (n = 189)	≥ 14	0.96	0.93 – 0.99	0.77	0.98	0.89	0.96

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; AUC: Area under the curve; HC: Health control; MCI: Mild cognitive impairment; NPV: Negative predictive value; PPV: Positive predictive value

*Comprises of the ADAS-Cog 10-word immediate recall, 10-word delayed recall and word recognition.

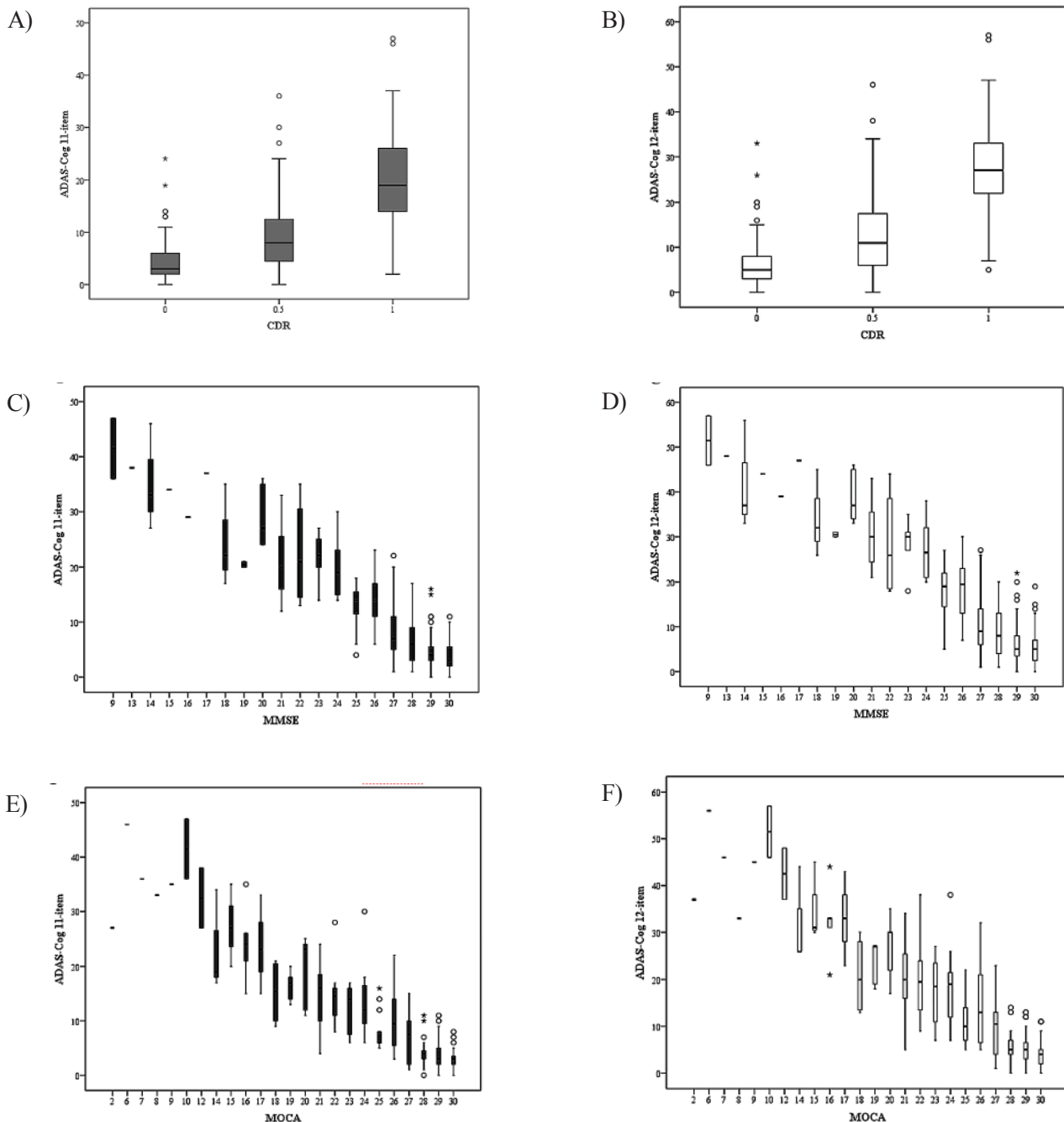


Fig. 1. Cross-sectional boxplots. A) shows the ADAS-Cog 11-item total error score with the CDR staging; B) shows the ADAS-Cog 12-item total error score with the CDR staging; C) shows the ADAS-Cog 11-item total error score with the MMSE; D) shows the ADAS-Cog 12-item total error score with the MMSE; E) shows the ADAS-Cog 11-item total error score with the MoCA; and F) shows the ADAS-Cog 12-item total error score with the MoCA. ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment

ADAS-Cog 11-item and 12-item Convergent Validity with MMSE and MoCA

The ADAS-Cog 11-item total error score showed good convergence with global cognition measures of MMSE ($\rho(269) = -0.75, P < 0.001$) and MoCA ($\rho(269) = -0.81, P < 0.001$) with large effect sizes.³⁴ Relatively smaller significant and negative correlations were observed with

the FAB ($\rho(269) = -0.67, P < 0.001$) (Table 4).

Comparatively, the ADAS-Cog 12-item error scores were inversely, and significantly related to the MMSE scores ($\rho(269) = -0.74, P < 0.001$) and MoCA scores ($\rho(269) = -0.81, P < 0.001$). Figures 1c to 1f illustrate the boxplots for the positive correlations between ADAS-Cog and the 2 global cognition measures.

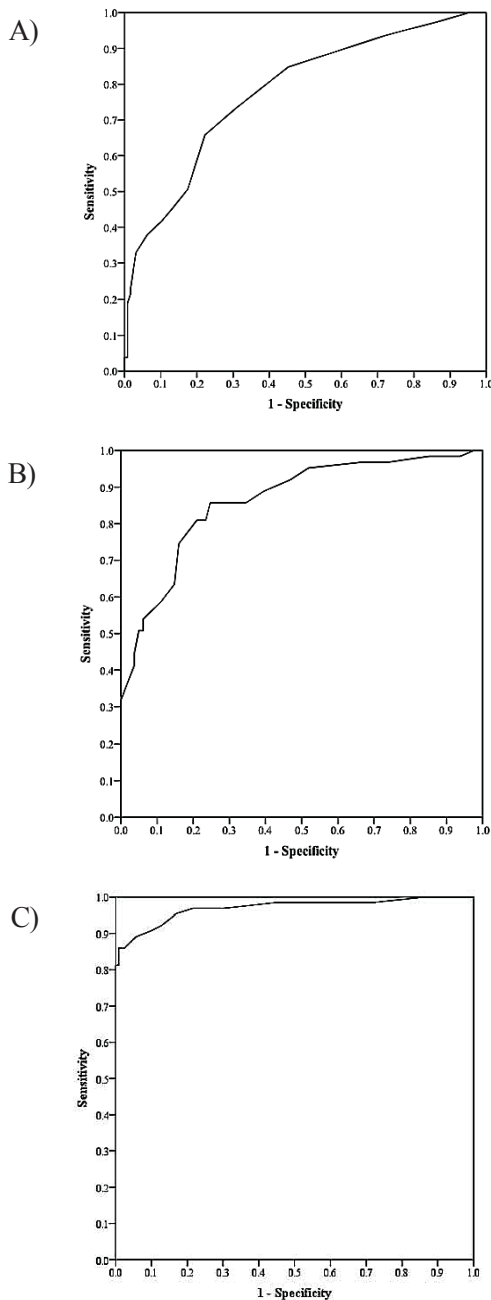


Fig. 2. ROC curves. A) shows the curve for differentiating between healthy controls and MCI patients for ADAS-Cog 11-items ($n = 205$); B) shows the curve for differentiating MCI from mild AD for ADAS-Cog 11-items ($n = 145$); and C) shows the curve for differentiating HC from mild AD for ADAS-Cog 11-items ($n = 189$). AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; HC: Healthy control; MCI: Mild cognitive impairment; ROC: Receiver operating characteristics

Selective Subtest Items

Spearman's correlation was also used to analyse which subtest items are highly correlated to the total ADAS-Cog score. Most subtest items showed moderate to large correlations ($\rho > 0.36$, all $P < 0.001$) with total ADAS-Cog score. Items that showed modest correlation are Ideational

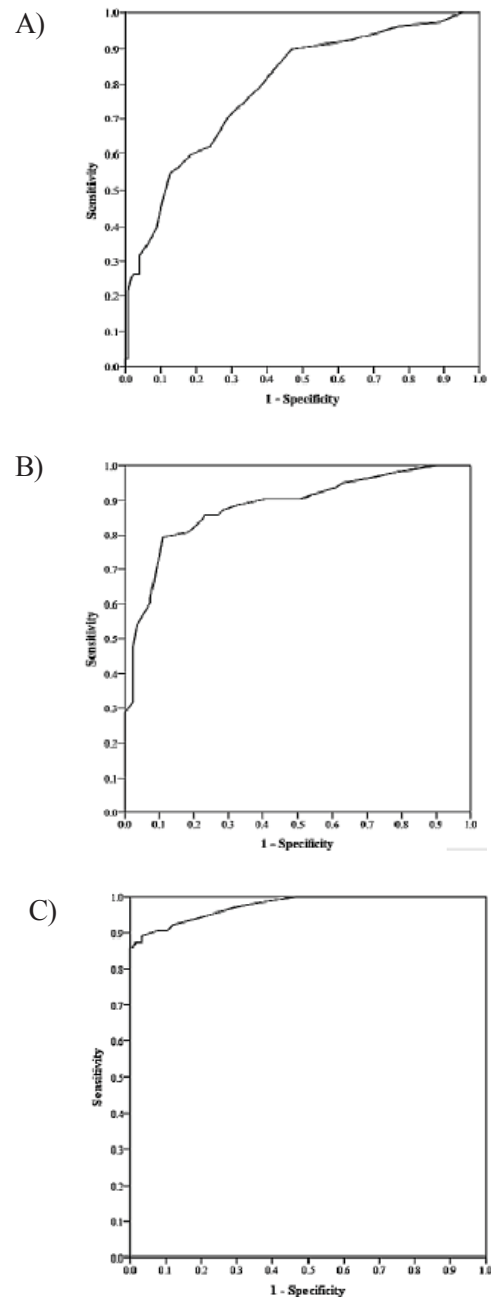


Fig. 3. ROC curves. A) shows a curve for differentiating between HCs and MCI patients for ADAS-Cog 12-items ($n = 205$); B) shows a curve for differentiating MCI from mild AD for ADAS-Cog 12-items ($n = 145$); and C) shows a curve for differentiating HCs from mild AD for ADAS-Cog 12-items ($n = 189$). AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; HC: Healthy control; MCI: Mild cognitive impairment; ROC: Receiver operating characteristics

Praxis, Naming, and Constructional Praxis ($\rho = 0.36$, $\rho = 0.49$ and $\rho = 0.53$ respectively). The 3 items that have the highest correlation with total ADAS-Cog score are Word Recall ($\rho = 0.83$), Word Recognition ($\rho = 0.79$) and 10-word Delayed Recall ($\rho = 0.78$). When these 3 subtest items were clustered as one and reanalysed, the correlation with the total ADAS-Cog score is very large ($\rho = 0.91$).

Table 4. Correlation between ADAS-Cog Total Error Score and Cognitive Measures

	ADAS-Cog 11 Item	
	$\rho(269)$	P Value
Overall ADAS-Cog and cognitive tests		
MMSE	-0.75	<0.001
MoCA	-0.81	<0.001
FAB	-0.67	<0.001
ADAS-Cog 11-item subtests and MMSE		
Recall	-0.69	<0.001
Commands	0.51	<0.001
Constructional praxis	-0.41	<0.001
Naming	-0.32	<0.001
Ideational praxis	-0.39	<0.001
Orientation	-0.62	<0.001
Recognition	-0.62	<0.001
Remembering instructions	-0.50	<0.001
Comprehension	-0.51	<0.001
Word-finding difficulty	-0.39	<0.001
Language	-0.42	<0.001
ADAS-Cog 11-item subtests and MoCA		
Recall	-0.74	<0.001
Commands	-0.50	<0.001
Constructional praxis	-0.50	<0.001
Naming	-0.33	<0.001
Ideational praxis	-0.35	<0.001
Orientation	-0.53	<0.001
Recognition	-0.62	<0.001
Remembering instructions	-0.53	<0.001
Comprehension	-0.60	<0.001
Word-finding difficulty	-0.46	<0.001
Language	-0.43	<0.001

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; FAB: Frontal Assessment Battery; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination

ADAS-Cog Internal Consistency

The ADAS-Cog demonstrated excellent internal consistency for the total scale (11 items; Cronbach $\alpha = 0.85$), total scale with delayed recall (12 items; $\alpha = 0.83$), and for the 3 subtests showing the highest correlation with the ADAS-Cog total score ($\alpha = 0.78$).

Given that the 3 subscales (Word Recall, Word Recognition, and 10-word Delayed Recall) demonstrated the largest correlation with the ADAS-Cog total score, we amalgamated the 3 subscale scores and labelled it to be the 'ADAS-Cog Episodic Memory' composite scale. Upon further analyses, ADAS-Cog Episodic Memory

composite scale appears to differentiate between MCI and mild AD patients (cutoff score: ≥ 14 , AUC = 0.87 (95% CI, 0.81 to 0.93); sensitivity = 0.76, specificity = 0.85, PPV = 0.97, NPV = 0.35) relatively better than between MCI and healthy controls (cutoff score: ≥ 6 , AUC = 0.73 (95% CI, 0.66 to 0.80); sensitivity = 0.61, specificity = 0.73, PPV = 0.86, NPV = 0.41). The optimal cutoff score to distinguish between HC and mild AD was ≥ 14 (AUC = 0.97 (95% CI, 0.94 to 0.99); sensitivity = 0.81, specificity = 1.00, PPV = 0.91, NPV = 1.00).

Discussion

This study presents evidence that ADAS-Cog is a sensitive tool to differentiate between cognitively intact and MCI, and between MCI and mild AD in a multicultural and multilingual Asian context of Singapore. The psychometric reliability and validity of the ADAS-Cog to detect MCI and mild AD withstands despite being conceptualised, designed and validated in the west.

ADAS-Cog 11-item and 12-item normative scores and psychometric analyses (AUC, sensitivity, specificity, PPV, and NPV) for MCI and mild AD for the local population were presented. The best ADAS-Cog 11-item cutoff score to differentiate between MCI and HC was ≥ 4 (sensitivity = 0.73, specificity = 0.69, PPV = 0.90, NPV = 0.40), while the best cutoff score to distinguish between MCI and mild AD was ≥ 12 (sensitivity = 0.86, specificity = 0.89, PPV = 0.99, NPV = 0.32). The excellent sensitivity, specificity, and PPV values implies that the ADAS-Cog may be useful in cognitive research settings, clinical trials and busy clinical settings involving healthy elderly, subjects with MCI and mild AD in the Asian context.

Noteworthy is the fact that the cutoff score of ≥ 4 on the ADAS-Cog 11 differed from prior literature showing a cutoff score of ≥ 6 . This may be explained by the fact that we found a mean score for ADAS-Cog 11 item of 3.99 ± 2.68 that was, on average, lower than the mean score of approximately 5.0 that was reported by Graham et al who used a purely Caucasian sample,¹⁷ Liu et al who assessed a low-education population,³⁸ as well as the mean score of about 5.5 that was found by Zec et al³⁹ and 5.6 that was found by Graham et al⁴⁰ who both recruited North American samples. It is plausible that the large sample of 125 healthy controls may account for the lower average error score on the ADAS-Cog 11.

Additionally, our findings are consistent with previous local^{19-21,27,29} and international validation studies¹⁵⁻¹⁸ that have reported associations between key sociodemographic variables and ADAS-Cog total error score. Lower levels of education affected ADAS-Cog performance ($r = -0.50$, $P < 0.001$).³⁸⁻⁴⁰ Younger elderly participants generally

performed relatively better on the ADAS-Cog ($r = 0.42$, $P < 0.001$)^{6,38-42} and males demonstrated modestly superior performance ($\rho = -0.33$, $P < 0.001$).³⁸ Self-reported depressive symptoms was higher in mild AD as compared to healthy controls but not MCI, suggesting that the neurodegenerative disease may exert a toll on the emotional well-being and quality of life of the patients albeit at the mild stage. In addition, the high proportion of non-Chinese in the mild AD patient group (23.44%) may imply that ethnic minorities are generally at-risk of cognitive impairment.

The ADAS-Cog items that presented with the lowest correlation with the ADAS-Cog total score include Ideational Praxis ($\rho = 0.36$) and Constructional Praxis ($\rho = 0.53$). These items measure apraxia; a person's impaired ability to conceptualise and carry out a familiar or learned complex task in a proper sequence despite neurologically intact motor function. According to DSM-V criteria, unusual non-amnesic presentations in major neurocognitive disorder (MCD) due to AD, such as apraxia, also exists but do not reflect the core symptom of MCD due to AD.⁴³ Languages disturbances, such as Aphasia, are also cognitive symptoms peripheral to the diagnosis of AD and are reflected by the modest correlation between subtest items that measure language and total ADAS-Cog 11-item scores (Naming: $\rho = 0.49$; Word Finding Difficulty: $\rho = 0.57$; Comprehension: $\rho = 0.65$; Spoken Language Ability: $\rho = 0.54$; Commands: $\rho = 0.57$).

This study also highlights that some subtest items in ADAS-Cog are highly correlated to its total score. A briefer version comprising of an amalgamation of subtests measuring episodic memory, specifically 10-word Immediate Recall, Word Recognition, and 10-word Delayed Recall therefore demonstrates usefulness in attending to patients with short attention span and difficulty focusing throughout the entire ADAS-Cog assessment. These 3 items evaluate the episodic memory and learning aspect of cognition, the key cognitive DSM-V criteria for MCD due to AD. As such, tests sensitive in detecting episodic memory impairment show good promise and should be recommended to facilitate the diagnosis of mild AD. Since ADAS-Cog assessment takes approximately 30-45 minutes to administer, a brief test with these 3 subtest items would be a preferred choice to be used in busy and time-constraint clinic settings and to avoid mental fatigue of the elderly patients.

While the literature generally showed an ADAS-Cog 11-item cutoff score of ≥ 6 ¹⁸⁻²¹ our study revealed a recommended cutoff score of ≥ 4 . This difference is likely a result of the mild nature of the dementia group in our study. The mean MMSE score in our patient group was 25.12 ± 4.36 which is reflective of the mild severity of dementia. The ADAS-Cog as a screening test will be more

useful for the detection of mild dementia due to a lack of ceiling effect. Hence, we believe that the ADAS-Cog will be most useful for the detection of mild dementia wherein the traditional screening tests such as MMSE will suffer from a ceiling effect.

Given that the results showed that the 3 subtests of the ADAS-Cog Episodic Memory scale were better at differentiating between persons with mild AD as compared to persons with MCI, it is thus recommended that the composite scale be used to screen for mild AD instead of MCI, though larger studies with participants with MCI and mild AD are required to shed further light on this. Several strengths and limitations of the study deserve mention. One of the strengths of the study was the recruitment of patients attending a tertiary neurology clinic who met the diagnosis of mild AD or MCI based on published criteria, therefore enabling the ADAS-Cog instrument to be used as a screening tool in clinical practice. Validation studies of screening tools that are helpful for screening for cognitive impairment and dementia in the Asian context are scarce, and this study attempted to fill this knowledge gap. Limitations include the cross-sectional design of the data that precludes the examination of the predictive validity of the tool to prognosticate disease progress. In addition, given that the ADAS-Cog scale was administered in either English or Mandarin, it may not be applicable to elderly persons who do not converse in either of the 2 languages. The number of tests administered in English were 202 (75%) and in Mandarin 67 (25%). The mean ($\pm$ SD) years of education for patients who took the test in English were 10.15 ± 3.94 and in Mandarin were 9.33 ± 6.40 . As such, we do not think language proficiency resulted in score differences. In addition, given that the 3 diagnostic groups comprised of mainly elderly persons of Chinese ethnicity, ethnic minorities are under-represented in the study. Future studies will need to recruit more ethnic minorities to ensure a representative sample that is more reflective of a diverse multicultural population. Future prospective validation studies may also explicate the optimal cutoff scores at baseline for predicting conversion from the prodromal MCI stage to AD pathology in the multicultural and multilingual Asian context.

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