Total Scores of the CERAD Neuropsychological Assessment Battery: Validation for Mild Cognitive Impairment and Dementia Patients With Diverse Etiologies

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Objectives: *This study aimed to validate the two total scores (TS-I and TS-II) of the Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery (CERAD-NP) for a large elderly population including mild cognitive impairment (MCI) and dementia patients with various etiologic backgrounds. The authors also investigated whether the addition of frontal-executive function score can improve the discrimination accuracy of the total scores for dementia and MCI.* **Design, Setting, and Participants:** *One thousand three hundred thirty-six normal comparison (NC), 583 dementia (420 AD, 111 non-AD dementia, and 52 mixed AD with non-AD dementia), and 250 MCI (223 amnestic and 27 nonamnestic MCI) individuals living in the community were included (all aged 60 years and older).* **Results:** *Both TS-I and TS-II were highly correlated with other global cognitive and functional scales. Both total scores showed, though modest, superior NC versus MCI discrimination ability to Mini-Mental State Examination (MMSE). Their discrimination ability for NC versus dementia was excellent and significantly better, especially in discriminating very mild dementia, than MMSE. The addition of frontal-executive test score to TS-I or TS-II did not make a significant improvement in dementia or MCI discrimination ability. Both of them also showed higher test-retest and interrater reliability than MMSE or any individual neuropsychological tests in the CERAD-NP.* **Conclusion:** *These results strongly support the validity and usefulness of CERAD total scores for early detection and progression monitoring of MCI and dementia in clinical and research settings.* (Am J Geriatr Psychiatry 2010; 18:801–809)

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The Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery (CERAD-NP) is a very widely used cognitive test packet for the evaluation of patients with Alzheimer disease (AD) and other dementia.[1–3] Although the CERAD-NP consists of several subtests, such as Verbal fluency (VF), modified Boston Naming Test (BNT), Mini-Mental State Examination (MMSE), Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), Constructional Praxis (CP), and Constructional Recall (CR), it originally provides only individual test scores, but not total score, which would be very useful for detection and progression monitoring of cognitive impairment.

One recent study proposed a total score for the CERAD-NP, which was calculated by summing the scores of six tests in the CERAD-NP except MMSE and CR. Although the proposed total score was reported to have good reliability and validity for AD and amnestic mild cognitive impairment (MCI) (aMCI) patients,[4] it has not been validated for non-AD dementia or nonamnestic MCI (naMCI) patients. Non-AD dementia, especially vascular dementia (VD) and dementia with Lewy Bodies (DLB), are very common in both clinical and community setting.[5–8] NaMCI is known to be more related to non-AD dementia, whereas aMCI is regarded as a preclinical state of AD.[9] Therefore, the total score needs to be validated further for the elderly including non-AD dementia and naMCI patients, to be used in real clinical or epidemiologic situation.

In addition, in terms of encompassed tests to generate total score, the proposed one does not included CR, although the recent version of the CERAD-NP includes CR as a unique visuospatial memory measure. Therefore, it is also needed to examine whether adding CR score to the proposed total score can increase the validity or not.

In this study, we first aimed to validate the previously proposed CERAD total score (total score I [TS-I]) further for a large number of elderly people including non-AD dementia and naMCI as well as AD and aMCI. Second, we compared the validity of TS-I with that of a new total score (total score II [TS-II]), which is generated by adding CR score to TS-I. We also investigated whether the addition of frontal-executive function scores can improve the discrimination accuracy of TS-I or TS-II for dementia and MCI patients. The CERAD-NP does not include any specific frontal-executive function test,[3] which may lower the discrimination ability of TS-I or TS-II, especially for non-AD dementia and naMCI, in which frontal-executive dysfunction is more prominent than in AD or aMCI.

METHODS

Subjects

Study subjects were recruited from the pool of elderly individuals registered in a program for the early detection and management of dementia at nine centers located in Seoul and Kyunggi and Kyungsang province of Korea (two public health centers, six dementia or memory clinics, and one senior citizens welfare center) from November 1996 to April 2008. In this study, 583 patients with dementia, 250 patients with MCI, and 1,386 normal comparison (NC) individuals were included. All subjects lived in the community and aged 60 years and older. A diagnosis of dementia was made according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders.[10] AD was diagnosed according to the probable or possible AD criteria of the National Institute of Neurological and Communication Disorders and Stroke/AD and Related Disorders Association (NINCDS-ADRDA).[11] VD was diagnosed according to the probable or possible VD criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN).[12] DLB or Parkinson disease dementia (PDD) was diagnosed according to the DLB consensus criteria[13] and frontotemporal dementia

(FTD) was diagnosed according to the FTD consensus criteria.[14] MCI was diagnosed according to current consensus criteria.[9] All MCI individuals had an overall clinical dementia rating scale (CDR)[15] of 0.5. All NC subjects received a CDR[15] score of 0. The exclusion criteria for all subjects were any present serious medical, psychiatric, and neurologic disorders that could affect the mental function; evidence of focal brain lesions on magnetic resonance image; the presence of severe behavioral or communication problems that would make a clinical examination difficult; an absence of a reliable informant; and inability of reading Korean (i.e., inability of reading 10 words in WLM from the CERAD-NP). Individuals with minor physical abnormalities (e.g., diabetes with no serious complications, essential hypertension, mild hearing loss, or others) were included. The Institutional Review Board of the Seoul National University Hospital, Korea, approved the study, and subjects or their legal representatives gave written informed consent.

Clinical and Neuropsychological Assessments

All subjects were examined by neuropsychiatrists with advanced training in neuropsychiatry and dementia research according to the CERAD protocol. The CERAD clinical assessment battery included CDR,[15] Blessed Dementia Scale-Activities of Daily Living (BDS-ADL),[2,3] general medical examination, neurologic examination, laboratory tests, and brain MRI or computed tomography. Standard administration of the CERAD battery was previously described in detail.[2,3] Reliable informants were necessarily interviewed to acquire the accurate information regarding the cognitive, emotional, and functional changes and the medical history of the subjects. The eight tests included in the CERAD-NP (VF, BNT, MMSE, WLM, WLR, WLRc, CP, and CR) were applied to all study subjects by experienced clinical neuropsychologists or nurses. Two frontal-executive function tests (the Digit Span [DS] test from the Wechsler Adult Intelligence Scale-R[16] and the Stroop Color and Word Test [SCWT][17,18]) were additionally administered to 532 subjects (256 dementia, 122 MCI, and 254 NC). The Alzheimer's Disease Assessment Scale-cognitive items (ADAS-cog)[19,20] was also applied to 53 subjects (43 dementia, 5 MCI, and 5 NC). A Panel consisting of four neuropsychiatrists with expertise in dementia research made the clinical decisions including diagnosis and CDR after reviewing all the available raw data including the information for neuropsychological tests except ADAS-cog.

Calculation of Total Scores

Two CERAD-NP total scores, TS-I and TS-II, were calculated. TS-I is generated by simply summing the scores of six tests including the VF (maximum score 24), BNT (15), WLM (30), CP (11), WLR (10), and WLRc (10).[4] The maximum of TS-1 is 100 points. TS-II is calculated by adding CR score (maximum 11) to TS-I. Therefore, the maximum of TS-II is 111 points. Two composite total score (TS-I-E and TS-II-E) were also computed by adding frontal-executive score to TS-I and TS-II, respectively. Both color-word page score of the SCWT and DS backward score were used to calculate a frontal-executive score. Maximum color-word page score is originally 100 points, but the score was divided by five to be balanced with other test scores. The sum of adjusted color-word page score (maximum 20) and DS backward score (maximum 8) was used as a final frontal-executive score (maximum 28).

Statistical Analysis

Concurrent validity was determined by using Pearson correlation analysis. Test-retest reliability was determined by using intraclass correlation. Receiver operating characteristic (ROC) curve analysis was performed to investigate discrimination validity of the total scores. Area under the curve (AUC) of ROC curve was compared across the total scores and MMSE according to the method suggested by Hanley and McNeil.[21] The means of TS-I, TS-II, and MMSE score were also compared across CDR groups by using ANOVA and post hoc contrasts with Tukey Honestly Significant Difference method at the $p < 0.05$ levels.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of subjects are summarized in Table 1. Among the patients with dementia, 420 (72.0%) had AD; 111 (19.0%) non-AD dementia (65 [11.1%] VD; 10 [1.7%] DLB; 6 [1.0%] PDD; 6 [1.0%] FTD; and 24 [4.1%]

TABLE 1. Demographic and Clinical Characteristics of Study Participants

Characteristics	NC	MCI	Dementia	*F*	Tukey Post-Hoc Test
n	1,336	250	583		
Age M (SD), years	69.9 (5.8)	72.0 (6.2)	74.4 (7.0)	99.60[a]	A < B < C
Education, years	6.5 (4.9)	7.9 (5.2)	6.9 (5.6)	7.95[a]	A, B < B, C
% Women	67.2	64.0	67.4		
% CDR 0	100.0	0.0	0.0		
% CDR 0.5	0.0	100.0	21.6		
% CDR 1	0.0	0.0	54.2		
% CDR 2	0.0	0.0	19.9		
% CDR 3+	0.0	0.0	4.3		
CDR-SOB	0.0 (0.3)	1.22 (0.9)	6.7 (3.5)	2,420.90[b]	A< B < C
BDS-ADL	0.0 (0.2)	1.0 (0.8)	4.7 (2.6)	2,097.85[b]	A< B < C
MMSE	25.5 (3.1)	22.4 (4.1)	15.4 (5.7)	1,450.15[b]	A> B > C
TS-I	64.9 (10.7)	50.8 (11.3)	32.0 (12.8)	1,904.82[b]	A> B > C
TS-II	70.7 (12.6)	54.2 (12.9)	33.1 (13.7)	2,020.26[b]	A> B > C

Notes: CDR-SOB: Clinical Dementia Rating Sum of Box score; A: NC; B: MCI; C: dementia; < or >: a sign for statistical difference and its direction.

[a]p <0.001 by analysis of variance, *df* = 2, 2,166.

[b]p <0.001 by analysis of covariance controlling age and education as a covariate, *df* = 2, 2,164.

non-AD mixed dementia); and 52 (8.9%), mixed AD-VD dementia. MCI consisted of 223 aMCI (89.2%) and 27 naMCI (10.8%).

Concurrent Validity

Table 2 shows the results of correlation analyses between TS-I and TS-II, and MMSE, ADAS-cog, CDR-Sum of Box, and BDS-ADL score. Both TS-I and TS-II were significantly correlated with other scales.

Discrimination Validity

Between-Group Comparison of the Total Scores. TS-I and TS-II were significantly different among the NC, MCI, and dementia group after controlling age and education effect (Table 1). Post-hoc comparison showed that there was a significant mean score difference between any two groups.

NC Versus MCI Discrimination. Table 3 shows the results from ROC curve analyses for the investigation of discrimination validity of the total scores.

TABLE 2. Correlations[a] of the Two Total Scores With MMSE, ADAS-cog, CDR-SOB, and BDS-ADL in Total Sample

Tests	TS-I	TS-II	MMSE	ADAS-cog[b]	CDR-SOB	BDS-ADL
TS-I	1					
TS-II	0.99	1				
MMSE	0.86	0.86	1			
ADAS-cog	−0.81	−0.81	−0.80	1		
CDR-SOB	−0.76	−0.75	−0.77	0.77	1	
BDS-ADL	−0.74	−0.74	−0.75	0.66	0.95	1

Notes: CDR-SOB: Clinical Dementia Rating Sum of Box score.

[a]p <0.01 for all correlation by Pearson correlation analysis.

[b]ADAS-Cog was administrated to 53 subjects (43 dementia, 5 MCI, and 5 NC).

TABLE 3. AUCs and Cutoff Scores of TS-I, TS-II, and MMSE in NC, MCI, and Dementia Groups

	NC Versus MCI	NC Versus D	MCI Versus D
TS-I			
AUC	0.821[a]	0.970	0.863
SE	0.015	0.004	0.013
95% CI	0.792–0.850	0.962–0.978	0.845–0.888
Cut off	59.5	49.5	44.5[b]
Sen/Spe	79.2/71.0	90.1/91.8	84.0/72.0
TS-II			
AUC	0.822[a]	0.972	0.896
SE	0.014	0.004	0.012
95% CI	0.794–0.850	0.965–0.979	0.845–0.893
Cut off	66.5	53.5[b]	46.5[b]
Sen/Spe	84.0/64.7	91.6/90.6	82.7/72.8
MMSE			
AUC	0.722	0.941	0.838
SE	0.018	0.006	0.014
95% CI	0.687–0.757	0.929–0.953	0.810–0.866
Cut off	24.5[b]	21.5	20.5
Sen/Spe	66.0/65.5	85.6/90.0	81.5/69.6

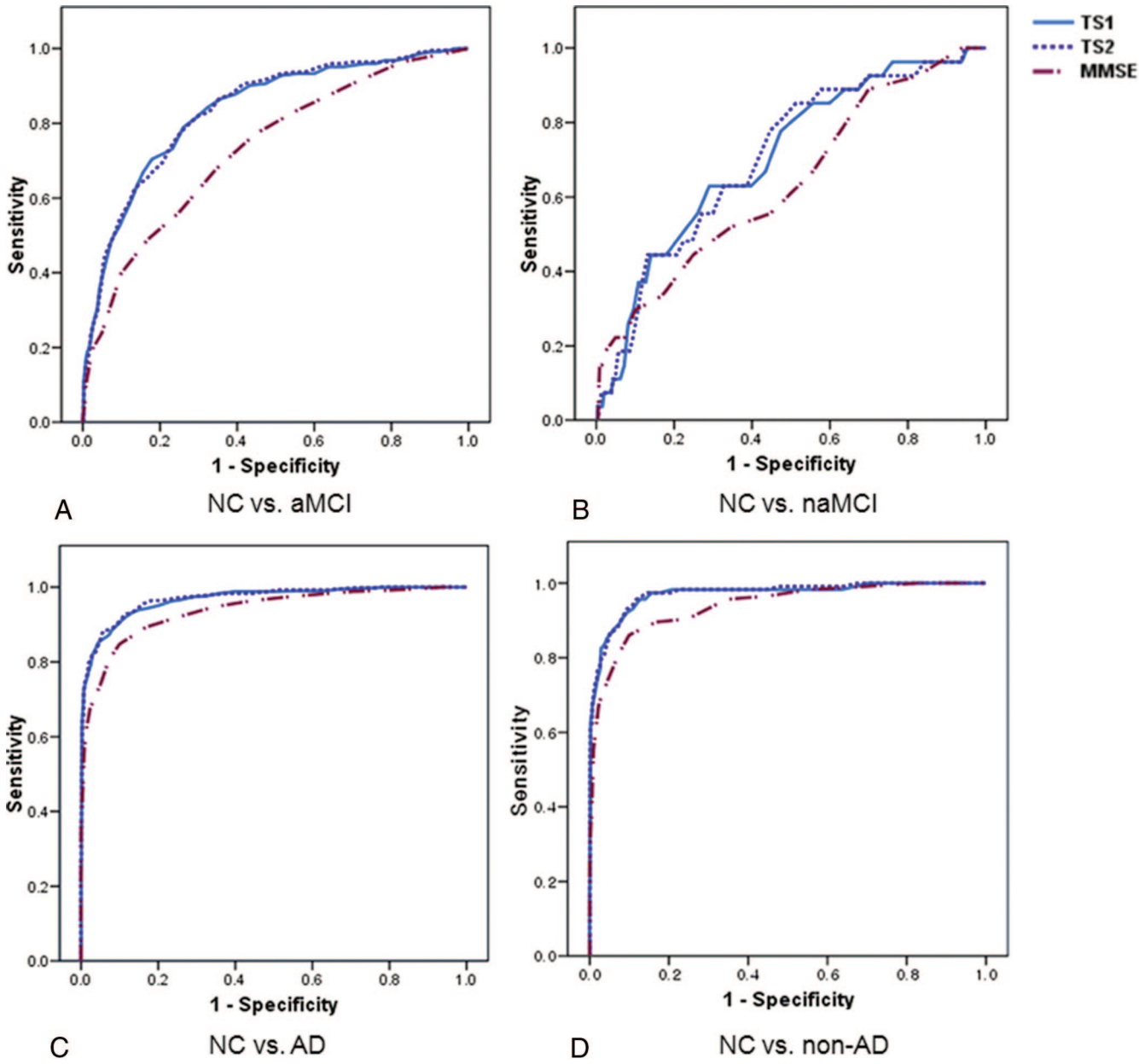
Notes: D: dementia; Sen/Spe: sensitivity/specificity.

[a]Significantly greater than that of MMSE, p <0.001 (tested by Hanley and McNeil's method[21]).

[b]Cutoff scores were slightly adjusted to have higher sensitivity than specificity, and the rests were optimal cutoff scores.

Although the discrimination accuracy of TS-I and TS-II for NC versus MCI was far from perfect (sensitivity/specificity: 79.2/71.0 for TS-I and 84.0/64.7 for TS-II), both of them showed significantly superior discrimination ability to MMSE (sensitivity/specificity: 66.0/65.5; $z = 5.15$, $p < 0.001$ for TS-I; $z = 5.30$, $p < 0.001$ for TS-II). For subgroup analysis, both total scores were also significantly better than MMSE in differentiating NC versus aMCI ($z = 5.119$, $p < 0.001$ for TS-I; $z = 5.220$, $p < 0.001$ for TS-II) (Fig. 1A). However, there was no significant difference of NC versus naMCI discrimination accuracy between the total scores and MMSE (Fig. 1B). There was no significant difference in NC versus MCI or NC versus

FIGURE 1. Receiver Operating Characteristic (ROC) Curves of CERAD Total Score I (TS-I), CERAD Total Score II (TS-II), and Mini-Mental State Examination (MMSE) Scores for [A] NC Versus aMCI, [B] NC Versus naMCI, [C] NC Versus AD, and [D] NC Versus Non-AD Discrimination



any subtype of MCI discrimination accuracy between TS-I and TS-II.

In addition, each of the two composite total scores, TS-I-E and TS-II-E, did not show significantly better discrimination ability even for NC versus naMCI as well as NC versus overall MCI or NC versus aMCI, than the corresponding CERAD total score (i.e., TS-I and TS-II, respectively).

NC Versus Dementia Discrimination. TS-I and TS-II were highly accurate in discriminating dementia from NC with above 90% sensitivity and specificity (Table 3). Both scores also had excellent discrimination ability not only for NC versus AD (Fig. 1C: AUC = 0.967 for TS-I; AUC = 0.970 for TS-II) but also for NC versus non-AD dementia (Fig. 1D: AUC = 0.969 for TS-I; AUC = 0.972 for TS-II). There was no significant difference in discrimination accuracy for NC versus dementia, NC versus AD or NC versus non-AD dementia among TS-I, TS-II, and MMSE (Table 3, Figs. 1C, D).

We also compared the discrimination ability of TS-I and TS-II with that of MMSE for dementia with different severities. Both TS-I and TS-II showed significantly better ability than MMSE for NC versus very mild dementia (CDR = 0.5) discrimination (Table 4: $z = 3.86$, $p < 0.001$ for TS-I; $z = 3.90$, $p < 0.001$ for TS-II). In contrast, in regards of NC versus mild (CDR = 1) or moderate to severe (CDR ≥ 2) dementia discrimination, there was no significant difference in accuracy between TS-I or TS-II and MMSE.

TS-I-E and TS-II-E did not show significantly better discrimination ability even for NC versus non-AD dementia, as well as NC versus overall dementia or NC versus AD, than the corresponding CERAD total score (i.e., TS-I and TS-II, respectively).

MCI Versus Dementia Discrimination. Both TS-I and TS-II showed relatively reasonable discriminating accuracy for MCI versus dementia (above 80% sensitivity and above 70% specificity) (Table 3). AUC comparison showed no significant difference in MCI versus dementia discrimination accuracy among TS-I, TS-II, and MMSE.

Dementia Interstage Discrimination. Both TS-I and TS-II showed significant difference across dementia stages based on CDR (F [4, 2,164] = 952.37, $p < 0.001$ for TS-I; F [4, 2,164] = 946.82, $p < 0.001$ for TS-II) and post-hoc comparison revealed that any adjacent two stages had significantly different TS-I and TS-II, indicating progressively worsening tendency according to CDR increase (Fig. 2). Similarly, MMSE also showed significant differences between any adjacent two stages. However, the effect size for the difference of score between CDR 0 versus CDR 0.5 was larger for TS-I or TS-II than for MMSE (1.57 [95% CI = 1.44–1.69] for TS-I, 1.57 [95% CI = 1.44–1.69] for

TABLE 4. AUCs and Cutoff Scores of TS-I, TS-II, and MMSE in NC and Dementia Groups

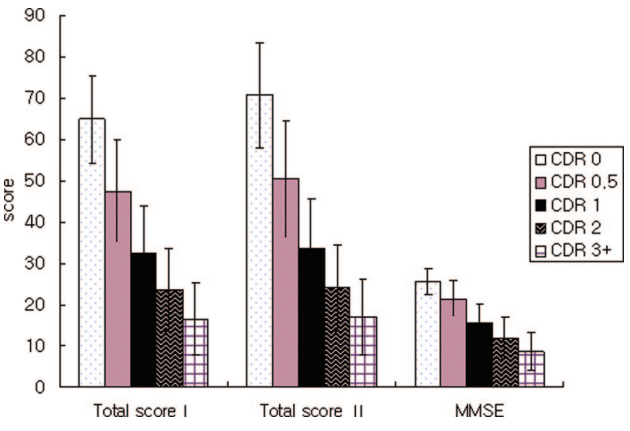
	NC Versus D0.5	NC Versus D1	NC Versus D2
TS-I			
AUC	0.930[a]	0.981	0.995
SE	0.012	0.004	0.002
95% CI	0.907–0.953	0.974–0.988	0.991–1.000
Cut off	54.5[b]	47.5	40.5
Sen/Spe	87.3/84.4	93.4/93.9	95.7/98.4
TS-II			
AUC	0.932[a]	0.983	0.996
SE	0.011	0.003	0.002
95% CI	0.910–0.955	0.977–0.989	0.992–1.000
Cut off	58.5	50.5	47.5
Sen/Spe	89.7/83.6	93.4/94.2	98.6/95.7
MMSE			
AUC	0.856	0.965	0.985
SE	0.018	0.005	0.006
95% CI	0.820–0.891	0.955–0.974	0.974–0.997
Cut off	22.5	21.5	19.5
Sen/Spe	71.4/83.2	92.1/90.0	94.3/95.1

Notes: D: dementia; D0.5: dementia with CDR 0.5; D1: dementia with CDR 1; D2: dementia with ≥CDR 2; Sen/Spe: sensitivity/specificity.

[a]Significantly greater than that of MMSE, $p < 0.001$ (tested by Hanley and McNeil's method[21]).

[b]All cutoff scores were optimal cutoff scores.

FIGURE 2. CERAD Total Score I, CERAD Total Score II, and Mini-Mental State Examination (MMSE) Scores According to the Dementia Severities Based on the Clinical Dementia Rating (CDR) Index



TS-II, and 1.16 [95% CI = 1.04–1.28[for MMSE). For any other two adjacent stages, there were no effect size differences between TS-I or TS-II and MMSE.

Reliability

The CERAD-NP was administered twice with a 1-month interval to 23 subjects (16 NC, 5 MCI, and 2 dementia) for test-retest reliability. Intraclass correlations between test and retest score were significant for both TS-I ($r = 0.87$, $p < 0.001$, 95% CI = 0.74–0.94) and TS-II ($r = 0.85$, $p < 0.001$, 95% CI = 0.68–0.93). The test-retest reliability of the MMSE for the same subjects was also significant, but the intraclass correlation coefficient was relatively lower ($r = 0.77$, $p < 0.001$, 95% CI = 0.52–0.89) than those of both total scores.

DISCUSSION

This study was conducted to validate CERAD total scores for a large elderly population including MCI and dementia patients with various etiologies. In terms of concurrent validity, both CERAD total scores, one not including CR score (TS-I) and the other including CR score (TS-II), showed high correlation not only with other representative global cognitive scale (i.e., MMSE and ADAS-cog) but also with widely used clinical severity scale (CDR-Sum of Box) and functional scale (i.e., BDS-ADL) scores. These findings suggest that both CERAD total scores can distinguish increasingly severe stages of dementia and have enough potential as a valid indicator for dementia or MCI progression monitoring. The fact that CERAD total scores showed similar MCI versus dementia discrimination and dementia interstage discrimination ability with MMSE also supports their validity as a good progression measure for dementing process from very early to advanced stage.

Although previous publication[4] reported that TS-I is an effective measure for screening AD, its ability for discriminating overall dementia or non-AD dementia from NC was not investigated. In this study, we included various types of non-AD dementia, such as VD, DLB, PDD, and FTD, as well as AD. Our results showed that both TS-I and TS-II are valid in distinguishing overall dementia or non-AD dementia, as well as AD, from NC. In other words, this implies that both CERAD total scores can be used as an excellent screening measure for dementia, regardless of its subtypes.

In terms of NC versus MCI discrimination, both CERAD total scores showed superior ability to MMSE, although their accuracy of discrimination is not so high. TS-I and TS-II also had better NC versus very mild dementia (CDR 0.5) discrimination ability than MMSE score, whereas there was no difference between TS-I or TS-II and MMSE score in regard of NC versus more severe dementia (CDR $\geq$1) discrimination. All these findings together indicate that CERAD total scores are more useful specifically for detecting individuals with very mildly impaired cognitive state (MCI or very mild dementia) in an elderly population than MMSE. This specific superiority of CERAD total scores to MMSE is probably related with a large percent of episodic memory score, which is well known as an earliest cognitive marker for AD process.[22] The proportion of episodic memory test (i.e., WLM, WLR, WLRc, or CR) score in TS-I and TS-II is 50% and 58%, respectively. Although individuals with pure non-AD dementia (19.0%) were included among overall patients with dementia, the patients with AD is about 80.9% if mixed AD-VD patients are classified as AD cases. In a similar vein, the superiority of CERAD total scores to MMSE was true only for NC versus aMCI discrimination (Fig. 1A) but not for NC versus naMCI (Fig. 1B) in which there is no prominent memory impairment.

TS-II including visual memory (CR) score did not have better ability in discrimination across NC, MCI, and dementia or progression monitoring of cognitive impairment than TS-I, which does not contain CR scores. Both total scores also showed quite similar discrimination ability even for non-AD dementia or naMCI, as well as AD or aMCI. These findings globally indicates that visual memory score itself does not make an additional contribution to the discrimination or progression monitoring of MCI or dementia patients, regardless of their etiologic background. Theoretically, some dementia or MCI patients with asymmetrically prominent right hemisphere pathology may, however, be better monitored or discriminated by TS-II than TS-I, although this possibility is not confirmed in this study. Therefore, in clinical setting, it is recommended that clinicians consider both CERAD total scores to make a better clinical

decision, if CR is administered with other CERAD tests.

The addition of frontal-executive score to each CERAD total score did not make a significant improvement in overall dementia or MCI discrimination. Contrary to our expectations, even when we focused only on non-AD dementia or naMCI discrimination, each composite score with frontal-executive component (TS-I-E or TS-II-E) showed no better discrimination accuracy than the corresponding CERAD total score (TS-I or TS-II). These findings may be explained by the following two possibilities. First, non-AD dementia or naMCI group is composed of individuals with very heterogeneous cognitive impairments, rather than with homogeneously prominent frontal-executive dysfunction like FTD patients. Therefore, the addition of some frontal-executive score did not make a statistically significant contribution to non-AD dementia or naMCI discrimination in general. Second, although the CERAD-NP was originally developed for AD assessment and is known to have a weak point in evaluating frontal-executive function, some neuropsychologic tests in the battery, such as VF, BNT, and WLR, measure partly frontal-executive function.[23–25] Therefore, CERAD total scores may already have relatively high discrimination ability not only for AD but also for non-AD, even before adding extra frontal-executive scores.

One-month test-retest reliability of TS-I and TS-II was higher than those of MMSE, when evaluated for the same subjects. In addition to the superiority to MMSE in regard of MCI and early dementia detection, this advantage in reliability further support better usefulness of both CERAD total scores in clinical and research settings than that of the MMSE, although the CERAD-NP requires more time and additional training to be applied.

In conclusion, our findings indicate that two CERAD total scores, one including CR score and the other not including CR score, are valid as a global cognitive measure for the detection and progression monitoring of MCI and dementia, regardless of their etiologic background. In particular, both of them have the advantage of well discriminating MCI or very mild stage of dementia from cognitively normal state, when compared with MMSE. Given their superior reliability to that of MMSE together, our results strongly support the usefulness of CERAD total scores in clinical and research settings, especially for early detection of dementia.

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