

MMSE Subscale Scores as Useful Predictors of AD Conversion in Mild Cognitive Impairment

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Purpose: This study was performed to examine the usefulness of subscores on the Mini-Mental State Examination (MMSE) for predicting the progression of Alzheimer's disease (AD) dementia in individuals with mild cognitive impairment (MCI).

Patients and Methods: A total of 306 MCI individuals in the Alzheimer's Disease Neuroimaging Initiative database were included in the study. Standardized clinical and neuropsychological tests were performed at baseline and at 2-year follow-up. Logistic regression analysis was conducted to examine the MMSE total and subscale scores to predict progression to AD dementia in MCI individuals.

Results: The MMSE total score and the MMSE memory, orientation, and construction subscores were inversely associated with AD progression after controlling for all potential confounders; MMSE attention and language subscores were not correlated with AD progression. The MMSE delayed recall score among the MMSE memory subscores and the MMSE time score among the orientation subscores, especially week and day, were inversely associated with AD progression; the MMSE immediate recall and place scores were not correlated with progression.

Conclusion: Our findings suggest that the MMSE memory, orientation, and construction subscores, which are simple and readily available clinical measures, could provide useful information to predict AD dementia progression in MCI individuals in practical clinical settings.

Keywords: mini-mental state examination, MMSE, mild cognitive impairment, MCI, Alzheimer's disease, AD, memory, orientation, construction

Introduction

Mild cognitive impairment (MCI) is classified as a transitional state between normal aging and mild dementia.¹ Longitudinal studies have found that the annual risk of conversion from MCI to probable Alzheimer's disease (AD) was 10–15%.^{2,3} Due to the high risk of conversion to AD, MCI has become a major concern for early detection of AD to initiate preventive measures. However, it is difficult to predict progression from MCI to AD, and a significant portion of MCI individuals remain stable or return to a normal cognitive state.^{4,5}

A number of studies have attempted to identify useful predictors of conversion from MCI to AD, including a number of neuropsychological markers,^{6–8} neuroimaging biomarkers,^{9–11} genetic markers,^{12–14} and biochemical markers^{15–18} alone and in various combinations.^{19,20} Especially, neuroimaging biomarkers, including magnetic resonance imaging (MRI) and positron emission tomography (PET) with fluorodeoxyglucose and beta amyloid tracers, showed high sensitivity and

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specificity.²¹ However, they are expensive, are feasible only in specialized medical centers,²² and are not appropriate for use in primary care settings, routine bedside check-ups, preventive health care settings, and large community-based studies.

It is important to identify a relatively simple, time-saving, and cost-effective predictor of AD conversion that can be easily used in a practical clinical setting. Previous studies suggested that the Mini-Mental State Examination (MMSE),²³ Clinical Dementia Rating (CDR) Sum of Boxes (CDR-SB),²⁴ and CDR orientation score²⁵ were good candidates for such a simple clinical predictor of AD progression. In this study, we examined the use of specific domains of the MMSE as potential markers of AD conversion. The MMSE has long been widely used as a tool to screen for cognitive impairment.²⁶ The MMSE total score comprises subscores representing each cognitive domain: memory, orientation, attention, language, and construction. Several studies have reported the usefulness of MMSE subscores. More rapid decline in the MMSE language subscore was observed in both language and behavioral variants of frontotemporal degeneration,²⁷ and MMSE subscores were helpful in differentiating between dementia with Lewy bodies and AD.²⁸

Not all domains of cognitive function deteriorate at the same time during the period of early cognitive changes in AD. In general, the decline of non-memory areas and related functions follow decline of episodic memory.²⁹ Therefore, specific MMSE domains other than memory may be useful for predicting conversion to AD in MCI individuals. However, little is known about this issue. This study was performed to investigate the usefulness of MMSE total and subscale scores for predicting AD dementia progression within a 2-year follow-up period in elderly individuals with MCI.

Materials and Methods

Study Design and Participants

Demographic information and clinical data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) database (<http://adni.loni.usc.edu>) on 2 February 2015. The ADNI was launched in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, and other biological markers along with clinical and

neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see <http://www.adni-info.org>. The study protocol was approved by the institutional review board of each participating site, and written informed consent was obtained from all participants. The complete list of ADNI sites' IRBs can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

From the ADNI-1 cohort, this study included 306 participants who were MCI at baseline evaluation and had at least one 2-year follow-up visit. All individuals with MCI met the current consensus criteria for amnesic MCI:³⁰ a memory complaint by the subject or their representative, objective memory loss measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. All of the MCI subjects had total MMSE scores of 24–30 and a CDR of 0.5. Details of inclusion and exclusion criteria for participants can be found at <http://www.adni-info.org>.

Baseline and Follow-Up Assessments

All participants underwent a standardized clinical evaluation based on the study protocol. Neurological assessments included the Alzheimer Disease Assessment Scale–Cognitive (ADAS-Cog),³¹ MMSE, and CDR-SB. The MMSE scores were divided into subscores for orientation, memory, attention, language, and construction. The data at baseline and 24 months were used to determine AD conversion, and subjects were considered to have progressed to AD if they met the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria for AD.³²

Statistical Analysis

The subjects were divided into two groups according to the clinical state at the 2-year follow-up evaluation: those who progressed to AD dementia (MCIp group) and those who did not (MCI_{np} group). Between-group comparisons for baseline continuous data, including demographic and clinical data, were performed using two-tailed *t*-tests. Baseline categorical data were analyzed by chi-square test or Fisher's exact test. Logistic regression analysis was performed to examine the ability of MMSE total or subscale scores to predict progression to AD dementia in

MCI individuals. For each analysis of the association between MMSE and progression to AD dementia, three models were tested for stepwise control of potential confounders. The first model did not include any covariates; the second model included age, gender, and education as covariates; and the third model included all potential covariates: age, gender, education, and CDR-SR. In all analyses, two-tailed p -values <0.05 were taken to indicate statistical significance.

Results

Presence of AD Progression Within 2-Year Follow-Up Period

All subjects ($n = 306$) were diagnosed with MCI at baseline assessments. After a 2-year follow-up, 111 (36.3%) had progressed to AD dementia (MCIp group), whereas the remaining 195 (63.7%) had not (MCIInp group) (Table 1).

Baseline Characteristics of AD Progression and Non-Progression Groups

The baseline demographics and clinical characteristics of the MCIp and MCIInp groups are shown in Table 1. There were no significant differences between the two groups with regard to age, sex, education, and CDR global score. The MCIp group had significantly higher CDR-SB scores and lower MMSE total and some MMSE subscores (memory, orientation, and construction) than the MCIInp group. In terms of the MMSE memory subscore, the MCIp group showed significantly lower MMSE delayed recall scores than the MCIInp group, but there was no significant difference in the MMSE immediate recall score between the two groups. With regard to the MMSE orientation subscore, there was a significant difference between the two groups in time subscore, but not in the place subscore. Among the MMSE time subscores, the week score of the MCIp group was significantly lower ($p = 0.008$) compared to those of the MCIInp group, and the time score was almost significantly lower ($p = 0.054$). However, there were no significant differences in other orientation subscale scores between the two groups.

Association of MMSE Total and Orientation Score with AD Progression

As shown in Table 2, MMSE total score and memory, orientation, and construction subscale scores showed

significant negative associations with AD progression after controlling for potential confounding variables, whereas attention and language score showed no such relations. Table 3 shows that the delayed recall score in the memory subscale scores and the time score in the orientation subscale scores were negatively associated with AD progression, whereas the immediate recall and place scores showed no such relations.

To assess the relationships of time subscale scores with AD progression, a series of logistic regression analyses were conducted in four steps (Table 4). In the first step, we tested one-item models: among the five models, the MMSE time-week (MMSE-W) model was statistically significant. In the second step, we tested two-item models, which included the MMSE-W model, and found that only the MMSE time-week and day (MMSE-WD) model was significant. In the third step, MMSE time-season, week, and day (MMSE-SWD) and MMSE time-month, week, and day (MMSE-MWD) were significant among the three-item models that included MMSE-WD. In the fourth step, all four-item models that included MMSE time-SWD or -MWD were significant.

Discussion

This study was performed to investigate whether specific MMSE domains are useful predictors of AD conversion in MCI individuals through a 2-year follow-up. This is the first longitudinal study using MMSE subscores to determine AD conversion among individuals with MCI. Our results showed that MMSE subscores for orientation and construction, as well as for memory, are useful predictors of conversion from MCI to AD.

As AD is characterized by a long preclinical period in which defects in episodic memory can be detected,³³ episodic memory decline is a well-known predictor of AD progression.³⁴ In accordance with these results, we showed that the MMSE delayed recall subscore predicted conversion to AD. Furthermore, our results showed that the MMSE time orientation subscore could be useful for predicting AD conversion in MCI. These results were consistent with a previous study showing that memory and temporal orientation were initial MMSE items that were lost during the course of AD.³⁵ Another study also demonstrated that the MMSE orientation for time predicted cognitive decline in elderly people.³⁶

In terms of the usefulness of the MMSE orientation score, one possible interpretation is that orientation consists of multiple cognitive domains, including attention

Table 1 Baseline Characteristics of the Amnesic MCI Group That Did Not Progress to AD Dementia (MCInp Group) and the Group That Did (MCIp Group) at 2-Year Follow-Up (n = 306)

	MCInp Group (n = 195)	MCIp Group (n = 111)	p-value
Age (Years)	74.75 ± 7.39	74.77 ± 7.07	0.984 [†]
Sex (Male/ Female)	127 (65.13)/ 68 (34.87)	69 (62.16)/ 42 (37.84)	0.603 [‡]
Education (Years)	15.79 ± 2.97	15.72 ± 2.85	0.831 [†]
CDR global score	0.5	0.5	
CDR sum of box	1.40 ± 0.70	1.84 ± 1.00	<0.001 [†]
MMSE total score	27.42 ± 1.72	26.62 ± 1.61	<0.001 [†]
MMSE subscale score			
MMSE memory score	4.96 ± 1.02	4.50 ± 1.10	<0.001 [†]
Immediate recall	2.96 ± 0.20	2.98 ± 0.19	0.323 [†]
Delayed recall	2.01 ± 1.00	1.51 ± 1.08	<0.001 [†]
MMSE orientation score	9.16 ± 1.00	8.86 ± 1.03	0.012 [†]
Time score	4.64 ± 0.66	4.39 ± 0.75	0.003 [†]
Year 0/1	5 (2.56)/ 190 (97.44)	2 (1.80)/109 (98.20)	1.000*
Month 0/1	3 (1.54)/192 (98.46)	4 (3.60)/107 (96.40)	0.260*
Week 0/1	13 (6.67)/182 (93.33)	18 (16.22)/93 (83.78)	0.008 [†]
Day 0/1	33 (16.92)/162 (83.08)	29 (26.13)/82 (73.87)	0.054 [†]
Season 0/1	17 (8.72)/178 (91.28)	15 (13.51)/96 (86.49)	0.187 [†]
Place score	4.52 ± 0.68	4.47 ± 0.69	0.503 [†]
Hospital 0/1	20 (10.26)/175 (89.74)	10 (9.01)/101 (90.99)	0.724 [†]
Floor 0/1	39 (15.38)/165 (84.62)	25 (22.52)/86 (77.48)	0.118 [†]
City 0/1	15 (7.69)/180 (92.31)	3 (2.70)/108 (97.30)	0.082*
Area 0/1	26 (13.33)/169 (86.67)	20 (18.02)/91 (81.98)	0.270 [†]
State 0/1	2 (1.03)/193 (98.97)	1 (0.90)/110 (99.10)	1.000*
MMSE attention score	4.73 ± 0.79	4.74 ± 0.72	0.908 [†]
MMSE language score	8.35 ± 0.57	8.35 ± 0.57	0.969 [†]
Naming 0/1/2	0 (0)/0 (0)/195 (100)	0 (0)/1 (0.90)/ 110 (99.10)	0.363*

(Continued)

Table 1 (Continued).

	MCInp Group (n = 195)	MCIp Group (n = 111)	p-value
Command 0/1/2/3	0 (0)/0 (0)/26 (13.33)/169 (86.67)	0 (0)/0 (0)/11 (9.91)/100 (90.09)	0.467*
Repetition 0/1	38 (19.45)/157 (80.51)	23 (20.72)/88 (72.28)	0.882 [‡]
Reading 0/1	0 (0)/195 (100)	1 (0.90)/110 (99.10)	0.363*
Writing 0/1	4 (2.05)/191 (97.95)	3 (2.70)/108 (97.30)	0.707*
MMSE construction score 0/1	17 (8.72)/178 (91.28)	21 (18.92)/90 (81.08)	0.012 [‡]

Notes: Data are presented as mean ± SD or number (%). [†] Student's t-test; [‡] chi-square test; *Fisher's exact test.

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

and visuospatial perception as well as memory.²⁵ Episodic memory impairment is the earliest symptom of AD, followed by attention and visuospatial dysfunction.³⁷ Individuals with MCI already have reduced memory performance,³⁸ so examination of orientation, which contains more information in addition to memory, may be more effective compared to examination of memory alone. In terms of orientation-related neural substrates, a clinicopathological study reported that both temporal and spatial disorientation in AD were related to neurofibrillary tangle densities in the hippocampus, superior parietal, and posterior cingulate cortex.³⁹ In contrast to this result, we found that place orientation could not predict AD conversion, whereas time orientation showed predictive capability. A previous PET study showed differences in the biological underpinnings of time and place orientation: time orientation was associated with the rate of glucose metabolism in the posterior cingulate gyri and right middle temporal gyrus, whereas place orientation was correlated with glucose metabolism in the right posterior cingulate gyrus.⁴⁰ Our results also suggested that time orientation may have specific neural substrates that are distinct from those for place orientation.

We found that the MMSE construction score was a valid predictor of AD conversion. The construction subscore was obtained using an interlocking pentagon copying item, which is given a maximum score of 1 point. The pentagon copying test is known to be an effective method for distinguishing between patients with dementia with

Table 2 Results of Multiple Logistic Regression Analysis to Assess the Relationships of MMSE Total and Subscale Scores with AD Progression at 2-Year Follow-Up in Individuals with MCI

	AD Progression at Two-Year Follow-Up	
	OR (95% CI)	P value
MMSE total score		
Model 1	0.758 (0.657 to 0.874)	<0.001
Model 2	0.754 (0.652 to 0.872)	<0.001
Model 3	0.787 (0.677 to 0.914)	0.002
MMSE subscale score		
Memory score		
Model 1	0.663 (0.531 to 0.829)	<0.001
Model 2	0.662 (0.530 to 0.828)	<0.001
Model 3	0.673 (0.534 to 0.847)	0.001
Orientation score		
Model 1	0.750 (0.597 to 0.943)	0.014
Model 2	0.751 (0.595 to 0.948)	0.016
Model 3	0.827 (0.649 to 1.055)	0.127
Attention score		
Model 1	1.018 (0.75- to 1.382)	0.908
Model 2	1.017 (0.745 to 1.388)	0.917
Model 3	1.037 (0.750 to 1.434)	0.826
Language score		
Model 1	1.008 (0.668 to 1.523)	0.969
Model 2	1.014 (0.670 to 1.534)	0.948
Model 3	0.972 (0.633 to 1.493)	0.898
Construction score		
Model 1	0.409 (0.206 to 0.814)	0.011
Model 2	0.405 (0.203 to 0.811)	0.011
Model 3	0.382 (0.186 to 0.783)	0.009

Notes: Model 1 did not include any covariates. Model 2 included age, sex, and education as covariates. Model 3 included age, sex, education, and CDR-SB score as covariates.

Abbreviations: OR, odds ratio; CI, confidence interval.

Lewy bodies from those with AD.⁴¹ Our results demonstrated the possibility of using the pentagon copying test as a screening tool for AD conversion. To complement the crude scoring method (0/1 score) and increase the ability to identify subtle differences, further studies using a wider range of scoring methods, eg, Bender-Gestalt test (0–4-point scores) or the Qualitative Scoring MMSE Pentagon Test (0–13-point scores),⁴² should be performed in the future.

The use of the MMSE subscores has a number of merits, including simplicity of administration and ease of

Table 3 Results of Multiple Logistic Regression Analysis to Assess the Relationships of MMSE Memory and Orientation Subscale Scores with AD Progression at 2-Year Follow-Up in Individuals with MCI

	AD Progression at Two-Year Follow-Up	
	OR (95% CI)	P value
MMSE memory-immediate recall score		
Model 1	2.060 (0.470 to 9.026)	0.338
Model 2	2.082 (0.467 to 9.289)	0.337
Model 3	2.090 (0.485 to 8.998)	0.322
MMSE memory-delayed recall score		
Model 1	0.639 (0.509 to 0.803)	<0.001
Model 2	0.639 (0.509 to 0.803)	<0.001
Model 3	0.648 (0.512 to 0.820)	<0.001
MMSE orientation-time score		
Model 1	0.612 (0.439 to 0.855)	0.004
Model 2	0.615 (0.439 to 0.860)	0.004
Model 3	0.689 (0.485 to 0.980)	0.038
MMSE orientation-place score		
Model 1	0.890 (0.635 to 1.249)	0.501
Model 2	0.900 (0.639 to 1.268)	0.548
Model 3	0.983 (0.689 to 1.403)	0.926

Notes: Model 1 did not include any covariates. Model 2 included age, sex, and education as covariates. Model 3 included age, sex, education, and CDR-SB score as covariates.

Abbreviations: OR, odds ratio; CI, confidence interval.

use and interpretation of the results. In addition, it is possible to obtain information about AD conversion through existing routine tests without additional tests. However, this study also has several limitations. The MMSE score is known to be highly affected by age, sex, and education.^{43,44} In general assessments, the normality of the MMSE total score was determined by using age-, sex-, and education-adjusted normative data; unfortunately, no such norms are available for the subscores of MMSE. However, these factors are unlikely to have affected the results of this study because we found no significant differences in age, sex, or education level between the MCip and MCInp groups, and the results remained significant after controlling for age, sex, and education. Another issue was that the NINCDS-ADRDA criteria were used to determine AD conversion, instead of using biomarkers of AD. The objective of the present study was to investigate predictors of AD conversion in a practical clinical setting, so we excluded these biomarkers. The importance of biomarkers in AD research is

Table 4 Results of Multiple Logistic Regression Analysis to Assess the Relationship of MMSE Time Subscale Scores with AD Progression at 2-Year Follow-Up in Individuals with MCI

	AD Progression at Two-Year Follow-Up	
	OR (95% CI)	P value
One item model		
MMSE time-season (S)		
Model 1	0.611 (0.292 to 1.278)	0.191
Model 2	0.610 (0.292 to 1.276)	0.189
Model 3	0.710 (0.329 to 1.534)	0.384
MMSE time-year (Y)		
Model 1	1.434 (0.274 to 7.518)	0.670
Model 2	1.451 (0.276 to 7.621)	0.660
Model 3	1.708 (0.310 to 9.394)	0.538
MMSE time-month (M)		
Model 1	0.418 (0.092 to 1.902)	0.259
Model 2	0.423 (0.093 to 1.936)	0.268
Model 3	0.504 (0.101 to 2.512)	0.403
MMSE time-week (W)		
Model 1	0.369 (0.173 to 0.786)	0.010
Model 2	0.369 (0.172 to 0.793)	0.011
Model 3	0.498 (0.226 to 1.098)	0.084
MMSE time-day (D)		
Model 1	0.576 (0.327 to 1.014)	0.056
Model 2	0.582 (0.329 to 1.029)	0.063
Model 3	0.626 (0.347 to 1.129)	0.120
Two items model with W		
MMSE time-SW		
Model 1	0.506 (0.303 to 0.843)	0.009
Model 2	0.508 (0.304 to 0.848)	0.010
Model 3	0.618 (0.362 to 1.056)	0.078
MMSE time-YW		
Model 1	0.463 (0.233 to 0.918)	0.027
Model 2	0.465 (0.232 to 0.929)	0.030
Model 3	0.618 (0.301 to 1.268)	0.189
MMSE time-MW		
Model 1	0.400 (0.205 to 0.779)	0.007
Model 2	0.402 (0.205 to 0.787)	0.008
Model 3	0.514 (0.255 to 1.037)	0.063
MMSE time-WD		
Model 1	0.526 (0.341 to 0.812)	0.004
Model 2	0.527 (0.339 to 0.818)	0.004

(Continued)

Table 4 (Continued).

	AD Progression at Two-Year Follow-Up	
	OR (95% CI)	P value
Model 3	0.603 (0.382 to 0.953)	0.030
Three items model with WD		
MMSE time-SWD		
Model 1	0.572 (0.398 to 0.822)	0.003
Model 2	0.574 (0.398 to 0.827)	0.003
Model 3	0.649 (0.443 to 0.951)	0.026
MMSE time-YWD		
Model 1	0.564 (0.372 to 0.856)	0.007
Model 2	0.565 (0.371 to 0.863)	0.008
Model 3	0.650 (0.419 to 1.009)	0.055
MMSE time-MWD		
Model 1	0.536 (0.356 to 0.806)	0.003
Model 2	0.536 (0.354 to 0.812)	0.003
Model 3	0.608 (0.394 to 0.938)	0.024
Four items model with S(or M)WD		
MMSE time-SYWD		
Model 1	0.600 (0.422 to 0.853)	0.004
Model 2	0.602 (0.422 to 0.858)	0.005
Model 3	0.682 (0.470 to 0.989)	0.043
MMSE time-SMWD		
Model 1	0.589 (0.418 to 0.829)	0.002
Model 2	0.591 (0.418 to 0.834)	0.003
Model 3	0.661 (0.461 to 0.947)	0.024
MMSE time-YMWD		
Model 1	0.568 (0.383 to 0.843)	0.005
Model 2	0.570 (0.382 to 0.849)	0.006
Model 3	0.649 (0.427 to 0.986)	0.043

Notes: Model 1 did not include any covariates. Model 2 included age, sex, and education as covariates. Model 3 included age, sex, education, and CDR-SB score as covariates.

Abbreviations: OR, odds ratio; CI, confidence interval.

growing, and the ADNI study included comprehensive measures of biomarkers, such as MRI, FDG, and amyloid PET. Outside the practical clinical setting, further research using biomarker changes as outcome variables in addition to clinical AD conversion is required. Finally, we used only 2-year follow-up data to investigate the earliest predictors of AD conversion within a short period. However, further studies with a longer follow-up period are required.

Conclusion

Our findings emphasize the importance of assessing orientation and construction domains to identify subjects at high risk of AD conversion among elderly people whose memory function is already impaired. In terms of simplicity, rapid administration, and ease of interpretation, MMSE subscales of memory, orientation, and construction could be useful screening tools for predicting conversion to AD from MCI in practical clinical settings.

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Disclosure

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