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Risk Classification in Mild Cognitive Impairment Patients for Developing Alzheimer's Disease

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Abstract. The objective of this study was to develop new risk classifications for conversion to Alzheimer's disease (AD) by comparing the relative reliability of classifiers in patients with mild cognitive impairment (MCI). The 397 MCI subjects and all baseline data, including characteristics, neuropsychological tests, cerebrospinal fluid biomarkers and MRI findings in Alzheimer's Disease Neuroimaging Initiative (ADNI), were used for analysis by Cox proportional hazard regression, bootstrap sampling, and c-index. Multivariate Cox regression analysis revealed the following factors to be associated with increased risk of conversion from MCI to AD during the 53-month follow-up period: AVLT 30-minute delayed recall, AVLT trial 1, Boston naming, logical delayed recall, trail-making B, CDR-sob, ADAS13, the cortical thickness of the right inferior temporal lobe (st91ta), and the left hippocampus volume. The combinations of ADAS13 at a cutoff point of 15.67 with CDR-sob at 1.5 or with the cortical thickness of the right inferior temporal lobe at 2.56 mm^3 produced high conversion rates of 92.7% (82.4%–100.0%) and 88.8% (77.3%–100.0%), respectively, at 48 months. The discriminative ability based on c-index for the proposed combination was 0.68. The sample size was estimated as 504 in the group with a combination of ADAS13 and CDR-sob whose conversion rate is highest. The combination of ADAS13 with CDR-sob at an optimal cutoff point has a high reliability in classifying the MCI patients into high- and low-risk conversion to AD and will be benefit for patients' assessment and potentially facilitate the clinical development of novel therapeutics.

Keywords: Alzheimer's disease, conversion, mild cognitive impairment, risk classification

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INTRODUCTION

With aging of the population, the prevalence of age-related diseases, as well as the cost of medicine and care, should increase, requiring nationwide approaches to reduce the social burden. Dementia, as represented by Alzheimer's disease (AD), is a leading cause of care-requiring status, which imposes a serious burden on society [1]. Recent advances in molecular science and imaging technologies have shed light on the etiological process of AD. However, preventive or therapeutic strategies have not yet been established.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Earlier detection and more accurate diagnosis of AD have been a major interest for all researchers in the field of AD. Enormous effort has been devoted to this investigation during recent decades. Research interests tend to focus primarily on the prodromal stage of AD, which is termed mild cognitive impairment (MCI). Subjects with MCI are of particular interest because they represent a population at particularly higher risk of converting to AD and a population in which primary prevention trials can be carried out [2, 3].

Although the use of cerebrospinal fluid (CSF) biomarkers and magnetic resonance imaging (MRI)/positron emission tomography (PET) for early AD detection in routine medical practice is recommended based on all the achievements obtained [4, 5] and the latest diagnosis of MCI and AD published [6, 7], the application of these recommendations in clinical practice does not appear to be feasible.

Currently, the major challenges are to determine the optimal cutoff points for the tests and to compare their relative reliability, as reported by Petersen [8]. In this report, we use data of all MCI patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) followed-up for 53 months to explore the risk factors associated with the conversion from MCI to AD and then to elaborate a new risk classification for MCI patients using the optimal cutoff points and test combinations. Finally, we computed the sample size required to detect a hypothetical 25% change in AD incidence in a 24-month placebo-controlled randomized clinical trial by using the population at highest risk.

METHODS

Subjects

All data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Written informed consents were obtained from the subjects at each of the participating centers.

Genetics

Details of the genotyping methods have been published. For each individual, we downloaded the APOE genotype.

MRI

MRI was performed using standardized protocols on 1·5T MRI units with 3D T1-weighted sequences optimized for the different scanners as indicated at http://adni.loni.ucla.edu/about-data-samples/image-data/ [9]. All images were corrected for spatial distortion due to gradient nonlinearity and normalized for B1 non-uniformity (also http://adni.loni.ucla.edu/about-data-samples/image-data/). MRI measures were reconstructed with the software program *Freesurfer* as previously described in detail [10]. Automated 3D whole-brain segmentation procedure [10, 11] was used. The processing included automated Talairach space transformation, intensity inhomogeneity correction, intensity normalization, tissue segmentation (the subcortical structures, brain stem, and cerebral cortex) [11, 12], automated correction of parcellation of the cerebral cortex [13] and topology defects, and surface deformation to form the gray/white matter boundary and gray matter/CSF boundary [12]. The cortical thickness average, standard deviation of thickness, surface area, and cortical volume were calculated as features. The automated HMAPS method was also used to measure several structures such as hippocampal volume.

Analysis data-set

We downloaded data from LONI (http://adni.loni.ucla.edu) on 15 November 2010. Only MCI patients were included in the analysis; all the assessments at baseline and the outcomes within 53 months were extracted. The factors included in analysis are as follows. The neuropsychological tests performed included the Mini-Mental State Examination (MMSE); Clinical Dementia Rating Scale-sum of box (CDR-sob); Alzheimer's Disease Assessment Scale with 13 items (ADAS13); auditory verbal learning test (AVLT), which includes 8 subscores (AVTOT1-6), AVLT delayed recall (AVDEL), AVLT 30-minute delayed recall (AVDEL30); verbal fluency (animal, CATANIMA and vegetable, CATVEGE); logical memory (which includes two parts: immediate (LIMMTOTAL) and late recall (LDEL); Boston naming test

(BNT); digit span (DIGSCOR), digit symbol substitution (COPYSCO), Trail-making A (TRAA) and B (TRAB); clock drawing (CLOCK); age; gender; education; APOE; CSF tau; p-tau; and $A\beta_{42}$. The factors measured by MRI included the volume, cortical thickness, and surface area of the following regions: the left and right entorhinal cortex, left and right hippocampus, left and right inferior temporal lobe, left and right para hippocampus, and left and right superior temporal lobe. Left and right olfactory lobe, left and right hippocampus, and left and right para hippocampus by uaspmvbm method were also included.

Statistics

Cox proportional hazard regression models were used to identify the statistically significant variable used to create a given split or branch in the survival tree [14, 15]. First, we performed a univariate Cox regression analysis and selected factors with $p < 0.2$ to enter into the multivariate Cox regression analyses with stepwise variable selection. Factors selected by multivariate regression ($p < 0.05$) were then divided into two groups by a cutoff that produced a maximum log-rank test statistic for AD incidence. These binary-transformed variables were assessed in the survival tree. For survival tree analysis, we set the two splitting-rules, i.e., $p < 0.05$ and sample size of each subgroup in a tree was more than 50.

In one hundred survival trees made by bootstrap samples, the first frequent combinations were determined by numbered ranking of first- and second-level factors in the branches and trees. The selected combinations were used to classify the MCI patients using the Kaplan-Meier method to estimate survival curves, and curves were compared by a two-sided log-rank test. Probability of remaining AD free was presented as the 12-, 24-, and 48-month point estimate. Furthermore, discriminative ability was assessed with the concordance index (c-index), which is the proportion of all pairs of subjects whose survival time can be ordered so that the subject with lower risk is the one who survived longer [16]. Statistical analyses were done by using SAS version 9.1(SAS Institute, Inc., Cary, NC, USA) and R version 2.12.1 with the party, CPE and Design libraries.

With using subjects from the high-risk subgroups identified in the consensus trees, we computed sample sizes for clinical trial. The sample size required detected a hypothetical 25% change in AD incidence (1-probability of remaining AD free) at 24 months, using a two-armed analysis (log rank test) for 90% power and a 5% type I error rate, in the 24-month placebo-controlled randomized trial [17].

RESULTS

In total, 397 subjects with MCI at baseline were included. After almost 53 months of follow-up, 164 MCI subjects converted to AD. The annual crude conversion rate was 17.3%, 21.0%, 7.1%, and 1.0% in the 1st, 2nd, 3rd, and 4th year, respectively.

The mean age was 74.8 years (range: 55–90 years old); mean education was 157 years (range: 4.0–20.0). The number of male subjects was 256 (64.5%); the number of female patients was 141 (35.5%). We assume that the converted subjects were no longer followed after conversion. The median follow-up period was 27.0 months (range: 6.4–53.0 m).

Cox proportional hazard regression analyses

In univariate Cox proportional hazard regression analysis for time to conversion from MCI to AD, 57 factors were included; 41 factors with $p < 0.2$ were selected to enter into the multivariate Cox regression analysis (supplementary Table 1; available online: http://www.j-alz.com/issues/30/vol30-2.html#supplementarydata03).

After step-wise Cox regression analysis, the following factors were associated with a high risk of conversion from MCI to AD: MMSE, AVDEL30, AVLTOT1, BNT, CDR-sob, ADAS13, cortical thickness of the right inferior temporal lobe (st91ta), the left hippocampus volume (hippl), LDEL, and TRAB (Table 1).

Combination of the tests using optimal cutoff points

The optimal cutoffs for selected variables by stepwise Cox regression analysis were determined using a maximum log-rank permutation test. The values of the cutoffs are 1.5, 172 pg/ml, 2, 5, 26, 0.405 mm^3, 3, 15.67, 108, 1.78 mm^3, 3.08 mm^3, and 2.56 mm^3 for CDR-sob, $A\beta_{42}$, Avdel30, AVTOT1, BNT, hippl, LDEL, ADAS13, TRAB, cortex volume of the left entorhinal cortex (LVEntor), cortical thickness of left entorhinal cortex, st91ta, respectively.

In the analysis of 100 Cox trees by bootstrap sampling, the first two frequent factors at the first level in the 100 trees were ADAS13 (64) and logical memory with delayed recall (22). In the trees with ADAS13 as

Table 1
Factors associated with the conversion from MCI to AD (univariate and multivariate regression)

Factors	Univariate regression		Multiple regression	
	n	HR (95%CI)	*n*	HR (95%CI)
AVLT del30	381	0.80 (0.74–0.86)	316	0.90 (0.83–0.99)
AVLT total1	381	0.75 (0.67–0.83)	316	0.76 (0.66–0.86)
Boston naming	379	0.95 (0.92–0.99)	316	1.06 (1.02–1.12)
Logic memory delay recall	381	0.80 (0.75–0.85)	316	0.93 (0.86–1.00)
Trail-making B	381	1.01 (1.00–1.01)	316	1.00 (1.00–1.01)
CDR-sob	381	1.59 (1.35–1.86)	316	1.36 (1.13–1.64)
ADAS13	378	1.12 (1.09–1.15)	316	1.05 (1.02–1.10)
St91ta	333	0.17 (0.09–0.30)	316	0.31 (0.14–0.68)
Left hippocampus volume	366	0.004 (0.00–0.03)	316	0.03 (0.002–0.43)

AVLT del30: Auditory and verbal learning test: 30-minute delayed recall; St91ta: cortical thickness of the right inferior temporal lobe.

the first level, the top three factors at the second level were CDR-sob (29), volume of the interior temporal (14), and logical memory delayed recall (13). Therefore, the top three combinations: 29 (combination A), 14 (combination B), and 13 (combination C) were selected as risk classifiers. Combination A yielded a low-risk group (A1:ADAS13 $\leq$15.67), a moderate-risk group (A2: ADAS13 >15.67 and CDR-sob $\leq$1.5), and a high-risk group (A3: ADAS13 >15.67 and CDR-sob >1.5). Combination B was as follows: low risk (B1: ADAS13 $\leq$15.67), moderate risk (B3: ADAS13 >15.67 and st91ta >2.56 mm^3), and high risk (B2: ADAS13 >15.67 and st91ta $\leq$2.56 mm^3). Combination C was: low risk (C1: ADAS13 $\leq$15.67), moderate risk (C3: ADAS13 >15.67 and LDEL >3), and high risk (C2: ADAS13 >15.67 and LDEL $\leq$3). (Figs. 1A–C)

The incidence of AD among the entire cohort was 5.6% (3.2%–7.9%) at 12 months and 58.1% (95% CI: 50.2%–66.0%) at 48 months. The incidence of combination A3 was 12.9% (95% CI: 6.4%–19.2%) and 92.7% (95% CI: 82.4%–100.0%) at 12 and 48 months, respectively; for B2, these values were 10.6% (95% CI: 5.3%–15.8%) and 88.4% (95% CI: 76.7%–100.0%). The conversion rate was 70.7% (95% CI: 58.0%–83.4%) for $A\beta_{42}$ at 172 pg/mL and 78.4% (95% CI: 67.7–89.2%), as determined by left entorhinal cortex volume (LVEntor) of 1.78 mm^3 at 48 months of follow-up. The hazard ratios differed significantly among subgroups in every combination. The combination of ADAS13 with CDR-sob resulted in a higher conversion rate from MCI to AD than did by single $A\beta_{42}$ or MRI findings (Table 2, Fig. 2A–D).

Discriminative ability

We use c-index to assess the discriminative ability of classification of the combinations. The c-index was 0.68 (95% CI: 0.65–0.71) for combination A, 0.68 (95% CI: 0.65–0.71) for combination B, 0.68 (95% CI: 0.65–0·71) for combination C, 0.61 (95% CI: 0.56–0.66) for $A\beta_{42}$, and 0.63 (95% CI: 0.59–0.66) for MRI findings related to LVENtor.

Sample size estimation for prevention clinical trials on conversion from MCI to AD

We use AD incidence as the primary endpoint in the study population enriched by our risk classification (combination A) to calculate the sample size in randomized double-blind prevention clinical trials on AD over a 24-month follow-up period, which method can detect a 25% decrease in incidence.

Various sample size calculations were performed. The sample size was 504 for the estimation for combination A whose conversion rate was 54.1% at 24 months. The sample size was 556 for the estimation for combination B whose incidence was 53.3% at 24 months. The value was 956 in the population enriched by a single CSF protein ($A\beta_{42}$) and 884 when based on MRI findings related to LVENtor. The sample size was 1230 for subjects from the overall cohort whose conversion was 28.9% at 24 months.

DISCUSSION

There have been many papers and recommended diagnosis guidelines for MCI published based on data from the ADNI as well as from others [6, 7, 18–20]. However, the application of these guidelines to clinical practice and/or research purposes continues to represent a challenge.

The results based on the data obtained from the ADNI showed that compared with the CSF $A\beta_{42}$ test or MRI findings, the combination of ADAS-cog with several tests at optimal cutoff points yielded a better risk classification of MCI in terms of conversion from MCI

Table 2
AD incidence rate by combination and overall cohort at different time points

	Baseline	12th month		24th month		48th month		HR (95%CI)	C-index	Frequency/
	n	Conv.	Incidence % (95%CI)	Conv.	Incidence % (95%CI)	Conv.	Incidence % (95%CI)		(95%CI)	rank in 100 iterations
Average	381	21	5.6 (3.2–7.9)	102	28.9 (24.2–33.6)	161	58.1 (50.2–66.0)			
Combination A										
Low (A1)	124	2	1.6 (0.0–3.9)	11	9.2 (4.0–14.4)	22	23 (13.7–32.3)	1.0		
Moderate (A2)	147	5	3.5 (0.5–6.5)	36	27.5 (19.8–35.2)	64	61.8 (49.1–74.5)	3.2 (2.0–5.2)	0.68 (0.65–0.71)	29/1
High (A3)	110	14	12.9 (6.4–19.2)	55	54.1 (44.3–63.9)	75	92.7 (82.4–100.0)	6.9 (4.3–11.0)		
Combination B										
Low (B1)	124	2	1.6 (0.0–3.9)	11	9.2 (4.0–14.4)	22	23 (13.7–32.3)	1.0		
High (B2)	113	15	13.8 (7.3–20.3)	50	53.3 (43.0–63.7)	68	88.8 (77.3–100.0)	7.2 (4.5–11.7)	0.68 (0.65–0.71)	14/2
Moderate (B3)	144	4	2.8 (0.1–5.5)	41	29.4 (21.8–37.0)	71	68.0 (55.1–80.9)	3.4 (2.1–5.4)		
Combination C										
Low (C1)	124	2	1.6 (0.0–3.9)	11	9.2 (4.0–14.4)	22	23 (13.7–32.3)	1.0		
High (C2)	155	17	11.2 (6.2–16.2)	70	51.2 (42.7–59.7)	94	79.8 (69.5–90.1)	6.2 (3.9–9.8)	0.68 (0.65–0.71)	13/3
Moderate (C3)	102	2	2.0 (0.0–4.7)	21	21.8 (13.6–30.1)	45	69.2 (42.6–85.8)	2.9 (1.7–4.7)		
$A\beta_{42}$ (pg/ml)										
>172	60	1	2.7 (0.0–5.0)	9	16.5 (6.4–26.5)	12	29.8 (10.8–48.8)	1.0	0.61 (0.56–0.66)	
≦172	133	9	6.8 (2.5–11.2)	46	35.9 (27.6–44.3)	73	70.7 (58–83.4)	3.1 (1.7–5.6)		
VLEntor (mm^3)										
>1.78	148	3	2.0 (0.0–4.3)	23	16.2 (20.1–32.2)	38	32.9 (22.8–43.1)	1.0	0.63 (0.59–0.66)	
≦1.78	185	13	7.0 (3.3–10.7)	68	37.3 (30.6–44.8)	109	78.4 (67.7–89.2)	3.2 (2.2–4.6)		

Conv.: number of conversions from MCI to AD. VLEntor: volume left entorhinal cortex.

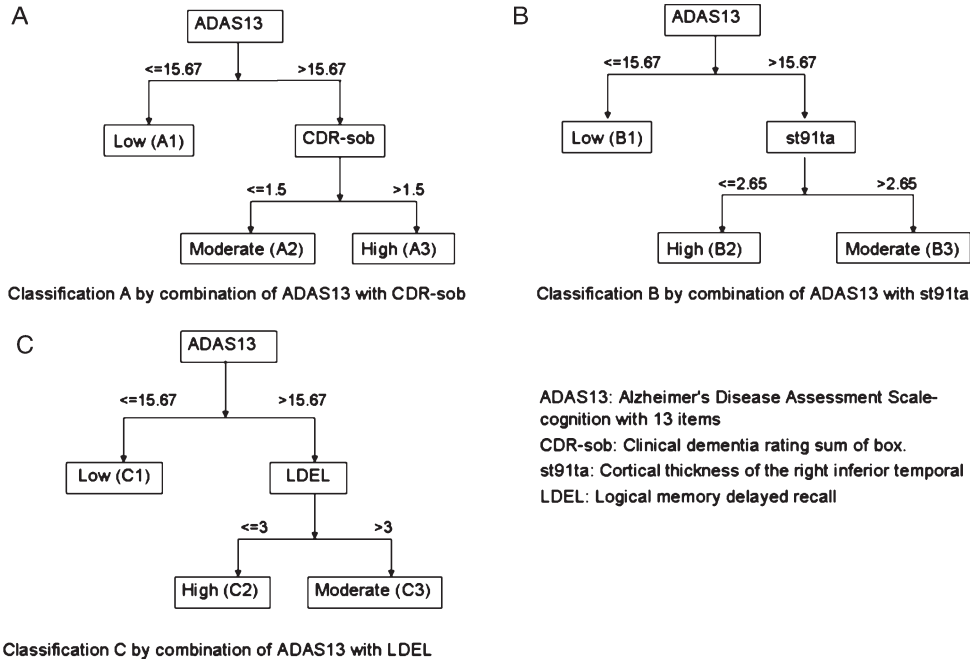

Fig. 1. Classification by different combinations of tests.

to AD. The combination of ADAS-cog at a cutoff point of 15.67 with CDR at 1.5 or the st91ta at 2.56 mm^3 resulted in the highest conversion (92.7% and 88.8%), while the conversion rate was 70.7% when determined based on $A\beta_{42}$ at 172 pg/ml and 78.4% by LVENtor at a cutoff of 1.78 mm^3 over a 48-month follow-up period. The c-indices used to measure the classification reliability were 0.68 for combination A and B, 0.61 for $A\beta_{42}$, and 0.63 for MRI findings.

Usually the threshold values used to classify the negative or positive risk group to predict conversion from MCI to AD were based on cutoff points discriminating AD from control health in cross-sectional studies. Such cutoff points are not appropriate as the threshold values to predict the conversion in prospective cohort study because the outcomes are different. We think the cutoff value of a test that produces a maximum log-rank test statistic for AD incidence is more reasonable to be applied to predict conversion. For example, the cutoff value of $A\beta_{42}$ at 172 pg/ml produced a higher HR (HR: 3.1, 95% CI: 1.7–5.6) than that based on 192 pg/ml (HR: 2.9, 95% CI: 1.4–5.1) suggested by Shaw [21].

The search for CNS biomarkers to combat today's most prevalent neurological diseases is reaching a fever pitch. With many new innovative strategies available to utilize these biomarkers, such as their use in diagnostic assay platforms, as intermediate surrogate endpoints and as therapeutics themselves, biomarker discovery and development provide multiple opportunities for the early diagnosis of neurological disorders. The CSF protein $A\beta_{42}$ and tau or MRI findings have been hypothesized to have potential utility in identifying patient populations that are most likely to benefit with the lowest risk of harm from new therapies [22–25]. Unfortunately, CSF $A\beta_{42}$ and tau protein are not the independent risk factors associated with the conversion from MCI to AD. Although the MRI findings were still the risk factors in multiple regression analysis, however, neither single tests nor combinations were selected as the final model because they provided no advantage in classifying MCI patients in terms of C-index or frequency in the context of 100 iterations of bootstrap sampling.

In accordance with previous reports [4, 5, 18, 20], MRI findings, such as the VLENtor, the cortical thickness of the left entorhinal cortex, and the volume of the left and or right hippocampus, were risk factors for the conversion from MCI to AD in our multivariate Cox regression analysis. However, our results did not support the use of such biomarkers in clinical practice for the early detection of AD or as screening tools for selecting patients in early-intervention clinical trials for accelerating drug discovery.

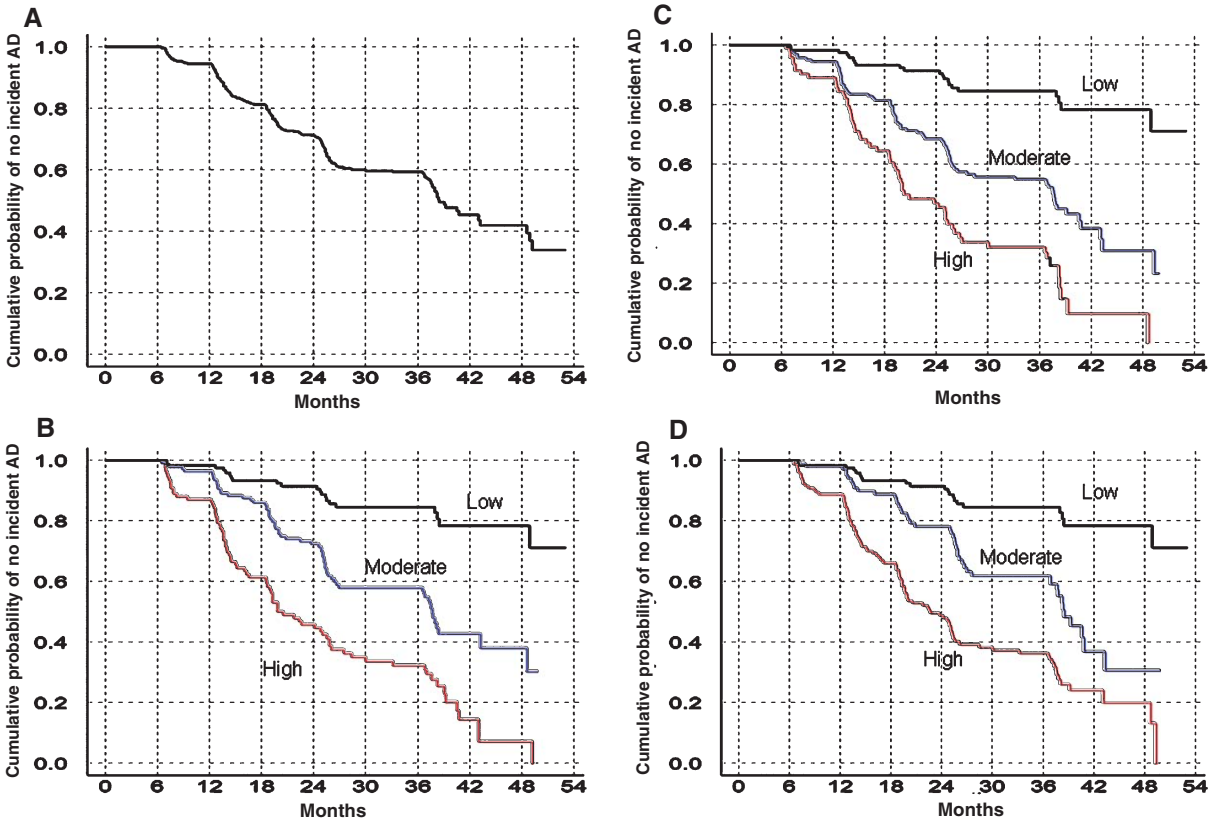

Fig. 2. Kaplan-Meier curves of conversion from MCI to AD by risk classifications of MCI. A) Conversion curve by overall cohort. B) Conversion curve by classification of ADAS13 and CDR. C) Conversion curve by classification of ADAS13 and st91ta. D) Conversion curve by classification of ADAS13 and LDEL.

Observational and interventional research on MCI and AD over recent decades suggests that prevention is more likely to succeed than efforts to cure. One important goal in AD research is to prevent brain cell damage and loss by intervening early in the disease process—even before outward symptoms are evident because by then it may be too late to effectively treat the disease. Randomized controlled trials have been conducted to test the efficacy of interventions specifically targeted individuals with early-stage dementia. Despite intensive research efforts, the pathogenesis and the natural history of AD remain unclear. In an effort to improve the quality of the results, clinical trial and translational research must optimize the approaches to patient selection, the timing of treatment, and sample size estimation. The enrichment methods employed in the current study may facilitate clinical development of new therapeutic technologies by dramatically reducing the sample size of clinical trials. Numerous studies have sought to estimate the sample size in clinical trials on MCI using different study populations and various primary endpoints [26, 27]. Notably, the conversion from MCI to AD is the only true end point in prevention clinical trials. Changes in ADAS-cog, CSF biomarkers, and neuroimaging markers are all surrogates endpoints that require further confirmation.

Although a c-index of 0.68 for the methods of classification is not high enough, the highest frequency in 100 trees predicts that, currently, it is the best method for classification compared with that utilizing single CSF $A\beta_{42}$ or MRI findings. Whether this enrichment strategy can be generally applied to other research studies remains to be confirmed.

To our knowledge, the patients with MCI in the ADNI are at the late stage of MCI, having a form of the disease that may be too advanced for biomarkers to be used for early detection. Therefore, more studies focusing on the patients with early-stage MCI and novel factors are needed to for early detection in neuropsychological tests and/or biomarkers and to standardize the related diagnostic criteria [28, 29]. The altered clinical presentation observed means that patients had

advanced to very early stages of AD, which clinical features as predictors have limitation. However, ADAS13 and CDR are not used in the diagnosis of MCI or AD. Before novel biomarkers are established as good predictors for early detection, the combination of ADAS13 and CDR-sob test can be used to effectively predict the progression from MCI to AD and be more appropriate as candidates for clinical application, such as subjects selection for prevention clinical trials on the conversion from MCI to AD and in research to clarify the manifestation and pathogenesis of AD.

Overall, the results indicate that the combinations of ADAS-cog at a cutoff point of 15.67 with CDR-sob at a cutoff point of 1.5 is highly reliable in classifying MCI patients as having a high or low risk of conversion to AD and is practicable. This approach is noninvasive and readily available in the clinic, and thus can improve patients' assessment and potentially facilitate the clinical development of novel therapeutics.

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