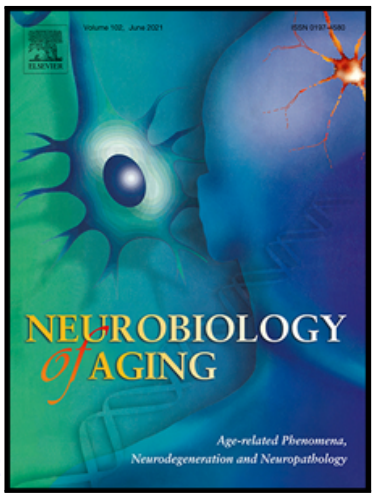

Development of prediction models for distinguishable cognitive trajectories in patients with amyloid positive mild cognitive impairment

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Highlights

- Three distinguishable trajectory subgroups were identified in Aβ+ participants with MCI
- Older age, presence of *APOE ε4*, higher Aβ deposition, and hypometabolism predict fast decline
- Prediction models showed good predictive accuracies in the development and validation data sets
- The predicted probability of belonging to a trajectory subgroup given the risk scores of each predictor was visualized

Development of prediction models for distinguishable cognitive trajectories in patients with amyloid positive mild cognitive impairment

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Abstract

The clinical outcomes of patients with amyloid beta-positive (Aβ+) mild cognitive impairment (MCI) are heterogeneous. We therefore developed prediction models for distinguishable cognitive trajectories in Aβ+ participants with MCI. We included 238 Aβ+ participants with MCI from the Alzheimer's Disease Neuroimaging Initiative to develop a group-based trajectory model and 63 Aβ+ participants with MCI from the Samsung Medical Center for external validation. Three distinguishable classes, slow decliners (18.5%), intermediate decliners (42.9%), and fast decliners (38.7%), were identified. Intermediate decliners were associated with older age, higher AV45 standardized uptake value ratios (SUVR) and lower fluorodeoxyglucose (FDG) SUVR than slow decliners. Fast decliners were associated with older age, presence of *APOE ε4*, higher AV45 SUVR and lower FDG

SUVR than slow decliners. Prediction models of cognitive decline showed good discrimination and calibration capabilities in the development and validation data sets. Our analysis yields novel insights into the cognitive trajectories of Aβ+ patients with MCI, which will facilitate their effective stratification in Aβ-targeted clinical trials.

Keywords: Mild cognitive impairment, amyloid β, Alzheimer's disease, group-based trajectory analysis model, prediction model

1. Introduction

The clinical outcomes of patients with mild cognitive impairment (MCI) are heterogeneous, and the rate of cognitive decline varies among patients (Amieva et al., 2005; Busse et al., 2006; Mungas et al., 2010). Although positron emission tomography (PET) findings suggest that patients with amyloid beta-positive (Aβ+) MCI are more likely to progress to dementia than their Aβ-negative counterparts (Okello et al., 2009), patients with Aβ+ MCI have different prognoses depending on biomarkers such as cerebrospinal fluid (CSF) tau level, tau deposition as assessed through tau PET images, hippocampal atrophy, and hypometabolism (Drzezga et al., 2003; Jang et al., 2019). These prognostic differences may result from the interaction of underlying pathologies with other multiple factors such as genetics and comorbidities (Jack et al., 2013). Consequently, previous studies have shown

that patients with Aβ+ MCI can be classified into converters and non-converters within three years from initial examinations (Jang et al., 2019; Okello et al., 2009). Therefore, determining the stratified disease prognosis among Aβ+ MCI patients is clinically essential for the early identification of individuals at risk of rapidly developing dementia due to Alzheimer's disease (AD). In fact, this patient population could significantly benefit from early treatment and therapies that are being tested in clinical trials.

The group-based trajectory analysis model (GBTM) is a statistical tool to analyze developmental trajectories over age or time, and it provides an estimated proportion of individuals that are likely to have similar longitudinal trajectories (Nagin, 2014). For example, group-based models have been applied to identify developmental trajectories among patients with amnestic and non-amnestic MCI (David et al., 2016; Lee et al., 2018). Even though predictive models of AD dementia have been generated using pattern classification methods based on clinical and imaging data as well as CSF biomarkers (Jang et al., 2019; Perrin et al., 2009), the GBTM method has not yet been utilized to determine the longitudinal cognitive trajectories of patients with Aβ+ MCI. A risk prediction model for disease progression is important for designing clinical trials and guiding clinical decision-making and early treatment administration. Therefore, we aimed to identify distinguishable cognitive trajectories among Aβ+ MCI patients and to develop a model that could predict the trajectory of each subgroup using risk factor-related data.

2. Materials and methods

2.1. Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu) and included participants from the ADNI-GO and ADNI-2

phases of the ADNI clinical trial. The goal of the ADNI is to utilize genetic, biomarker and clinical predictors of decline to identify the cross-sectional features and longitudinal trajectories that lead patients from normal aging to MCI and AD dementia. The inclusion and exclusion criteria of the ADNI database are defined in detail at http://adni.loni.usc.edu/methods/documents/.

In this study, we selected 420 participants with MCI. Patients were diagnosed with MCI according to the following criteria: subjective memory complaints with a Clinical Dementia Rating (CDR) score of 0.5, a Mini-mental state examination (MMSE) score of 24-30, absence of significant impairments in other cognitive domains, mostly preserved ability to carry out activities of daily living, and absence of dementia (Petersen et al., 2010). Early and late MCI were categorized according to the Logical Memory II subtest of the Wechsler Memory Scale. Specifically, early MCI was defined with a score of 0.5-1.5 standard deviations (SDs) below the mean of Cognitively Normal on delayed recall test, and late MCI was assigned with a score >1.5 SDs below the mean. (Aisen et al., 2010). After the baseline visit, the participants were followed up in 6- or 12-month intervals for clinical and neuropsychological assessments. At least three times throughout the study period, the patients underwent the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 13 questionnaire, brain imaging (fluorodeoxyglucose [FDG] PET, and 18F-AV-45 [Florbetapir] PET), and apolipoprotein E (*APOE*) genotyping.

2.2. Collection of clinical and multimodal biomarkers

Clinical data including demographic information, neuropsychological scores, and *APOE* genotyping were acquired from the ADNIMERGE dataset offered by the ADNI database. The ADAS-Cog-13 score, where higher scores reflect cognitive decline (Mohs et

al., 1997), was employed as a dependent measure for our longitudinal analyses. Additionally, we collected the average FDG and AV45 standardized uptake value ratios (SUVR) of AD signature brain regions at baseline (Jagust et al., 2009). The standardized imaging protocols have been previously described in detail (Jack et al., 2008; Landau et al., 2013).

MCI participants were divided into an Aβ+ and Aβ- group utilizing a SUVR >1.11 as the cut-off at baseline (Landau et al., 2013).

2.3. Data for external validation

The 63 participants with Aβ+ MCI from the Samsung Medical Center (SMC) were considered as data for external validation. These data were collected between September 2015 and March 2021. Instead of ADAS-Cog-13 scores, the Clinical Dementia Rating-Sum of Boxes (CDR-SOB) score was used as outcome variable, because the participants in the SMC did not complete the ADAS-Cog-13 test. All participants had been tested according to the CDR-SOB scale at least three times, and had also undergone 18F-florbetaben or flutemetamol PET for Aβ imaging.

We determined Aβ (+) employing the standardized visual assessments created by the companies that manufacture the amyloid tracers. In addition, Aβ uptake was quantitatively measured by scaling the Centiloid unit as described in previous studies (Battle et al., 2018; Rowe et al., 2017). To measure hippocampal volume, we employed an automated hippocampal segmentation method, which performs graph cut optimization, combined with atlas-based segmentation and morphological opening (Kwak et al., 2013).

2.4. Statistical analysis

In order to fulfill the aim of this study, we carried out the following four steps: 1) outlining trajectory subgroups according to longitudinal ADAS-Cog-13 scores, 2) comparing baseline demographic/clinical variables among the different trajectory subgroups, 3) constructing a prediction model for the trajectory subgroups, and 4) visualizing the prediction model through the baseline individual values of the predictive factors.

First, the GBTM was used to classify individuals into subgroups representing the progression of ADAS-Cog-13 score trajectories over time, so that individuals in the same subgroup had highly similar trajectories to one another, but not to those in other subgroups. In order to implement the GBTM, ADAS-Cog-13 scores were transformed using natural log because of the skewed distribution of the data after adding two to all scores to offset zero scores for log transformation. The average levels of ADAS-Cog-13 scores were modeled as a function of time and intercept, and the identified trajectory subgroups were labeled based on the slope. The proportion of the patient population following each trajectory was estimated based on the posterior probabilities of the subgroup memberships. Individuals were assigned to the trajectory subgroups based on the maximum posterior probability of group membership. The Bayesian Information Criterion (BIC) and the Sample Size-Adjusted BIC (SABIC) were applied to select the optimal number of subgroups and their order (Nagin and Odgers, 2010). A lower BIC (or SABIC) indicates a better fit. A difference of 6 or more BIC points between a (k-1) and a k-class model (k=2, 3,…) suggests that the additional number of classes meaningfully improves model fit (Kass and Raftery, 1995). Furthermore, to ensure the accuracy of subgroup classification, the average posterior probabilities of all model trajectories were investigated. Probabilities greater than 0.7 generally indicate acceptable classification (Nagin and Odgers, 2010). To further validate the adequacy of the identified trajectory subgroups, a bootstrap procedure with 1,000 iterations was employed (Efron and

Tibshirani, 1986). The GBTM was applied to each of the 1,000 bootstrap samples, and the difference between the value of each parameter, which was estimated from the original sample, and the bootstrap sample were calculated, and the 95% confidence interval (CI) was computed. For internal validation, the original dataset (238 participants) was split into a training and testing set according to a 6:4 ratio.

Second, continuous variables and categorical variables representing the baseline demographic, clinical, and genetic factors of each trajectory subgroup were compared using the Kruskal-Wallis test and the Chi-square test, respectively. For multiple comparison analysis, Tukey's test with ranks or Fisher's exact test with permutation method were performed for continuous and categorical variables, respectively.

Third, the prediction model for the trajectory subgroups was estimated using a multinomial logistic model. The linearity of the continuous variables to log odds of outcome in the model was investigated using a plot of log odd. Two categorical predictors were employed: sex (male and female, coded as 0 and 1, respectively) and *APOE ε4* genotype status (non-carriers and carriers, coded as 0 and 1, respectively). Furthermore, the two continuous variables of age and duration of education, which did not meet the linearity to log odds of outcome, were categorized into two groups (age: <70 years and ≥70 years, coded as 0 and 1, respectively; duration of education: <12 years and ≥12 years, coded as 0 and 1, respectively). The FDG and AV45 SUVRs were multiplied by ten in order to prevent an excessively large estimation of odds ratios (OR), and to estimate the ORs for a 0.1 increase in both the FDG and AV45 SUVRs.

Each model was assessed by adding variables in the following order: demographic variables, *APOE ε4* genotype status, and PET SUVR-related factors. We evaluated the fitness and predictability of each estimated model using the Akaike information criterion (AIC), Schwarz

Criterion (SC), R-square, M-index (Hand and Till, 2001), and polytomous discrimination index (PDI) (Van Calster et al., 2012). The goodness-of-fit of competing models was compered using the likelihood ratio test (LRT).

Finally, the predictor value of a specific patient was multiplied by the coefficient of the model corresponding to the predictor. When the model treated the slow decliners as a reference group, it resulted in the risk score of the predictor on a patient in the intermediate (fast) decliners. For intermediate (fast) decliners, the total risk score, obtained from the sum of all risk scores, was added to the value of the model's intercept to obtain a linear predictor. The probability of being classified as an intermediate (fast) decliner was estimated with a linear predictor utilizing the following formula:

$$\frac{exp(\text{linear predictor of intermediate (fast) decliners})}{[1+\exp(\text{linear predictor of intermediate (fast)decliners})+\exp(\text{linear predictor of fast decliners})}.$$

A bar graph was generated to display the risk scores of each predictor and the predicted probability of belonging to a trajectory subgroup given the individual's value of that predictor (Van Belle and Van Calster, 2015).

Continuous and categorical variables are summarized as the median (interquartile range [IQR], 1st - 3rd quartile), and frequency (percentage), respectively.

All the data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). For group trajectory analyses, the PROC TRAJ on SAS was employed (http://www.andrew.cmu.edu/user/bjones) (Jones et al., 2001). Graphical representation of the risk predictor model was carried out using the 'VRPM' package for R 3.6.1 (The R Foundation, Vienna, Austria). Two-sided p-values <0.05 were considered statistically significant.

3. Results

3.1. The demographic and clinical characteristics of the study participants

The demographics and clinical characteristics of the participants included in the ADNI and SMC datasets are presented in Table 1.

In the Aβ+ MCI participants from the ADNI, the median age was 73.2 years (IQR, 68.3-77.6 years). The median duration of education was 16 years (IQR, 14-18 years). Female participants accounted for 44.1% of all participants. *APOE ε4* carriers comprised 67.7% of all participants. The median ADAS-Cog-13 score was 16 (IQR, 12-21) and the median CDR-SOB score was 1.5 (IQR, 1-2) at baseline.

The median age of Aβ- MCI participants, who represented the reference group, was 69.4 years. In this group, female participants and *APOE ε4* carriers accounted for 46.2% and 24.7% of all participants, respectively.

In the SMC, the median age of Aβ+ MCI participants was 70 years (IQR, 65-77 years). Female participants and *APOE ε4* carriers account for 66.7% and were 68.3% of all participants, respectively. The median CDR-SOB score was 1.5 (IQR, 1.0-2.5) at baseline.

Table 1 The demographics and clinical characteristics of the participants in the ADNI and SMC

	ADNI		SMC
	Aβ+ MCI (n=238)	Aβ- MCI (n=182)	Aβ+ MCI (n=63)
Demographics			
Age, median (IQR), years	73.2 (68.3-77.6)	69.4 (63.6-75)	70 (65-77)
Age ≥70 years, N (%)	155 (65.4)	89 (48.9)	33 (52.4)

Female sex, N (%)	105 (44.1)	84 (46.2)	42 (66.7)
Education, median (IQR), years	16 (14-18)	16 (14-18)	12 (7-16)
Education >12 years, N (%)	196 (82.7)	164 (90.1)	25 (39.7)
Biomarkers			
APOE ε4 carriers, N (%)	161 (67.7)	45 (24.7)	43 (68.3)
Amyloid PET SUVR, median (IQR)	1.3 (1.2-1.5) †	1.01 (0.98-1.05) †	82.9(57.5-101.3) ‡
FDG PET SUVR, median (IQR)	1.2 (1.1-1.3)	1.3 (1.2-1.4)	
ADAS-Cog-13, median (IQR)	16 (12-21)	12 (8-16)	
CDR-SOB, median (IQR)	1.5 (1-2)	1.0 (0.5-1.5)	1.5 (1.0-2.5)

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; SMC, Samsung Medical Center; MCI, mild cognitive impairment; Aβ+, amyloid beta-positive; Aβ-, amyloid beta-negative; APOE, apolipoprotein E; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; PET, positron emission tomography; IQR, interquartile range, CDR-SOB, Clinical Dementia Rating-Sum of Boxes.

† AV45 PET; ‡18F-florbetaben or flutemetamol PET (Centiloid score)

3.2. Identifying distinguishable trajectory subgroups

In Aβ+ MCI participants, trajectories were grouped according to baseline (intercept) and slope (linear, quadratic) and the best classification was selected by model fit statistics. Three trajectory subgroups were labelled as slow, intermediate, and fast decliners based on the change of longitudinal ADAS-Cog-13 scores from the baseline (Fig. 1A). Two of the subgroups had quadratic trajectories and one subgroup had a linear trajectory (Fig. 1A, Table 2). For these trajectories, the BIC values were 840.9 (n=1286) and 825.7 (n=238), while the SABIC values were 820.3 (n=1286) and 801.8 (n=238). The average posterior probability for each trajectory subgroup was 98.5, 93.6, and 96.3, respectively (model 6) (Table 2). The parameter estimates of the model were highly similar between the original and bootstrap samples, suggesting that the trajectory subgroups identified in the original sample were stable (Table 3).

Quadratic patterns for 44 slow decliners (18.5%) and 102 intermediate decliners (42.9%), as well as a linear pattern for 92 fast decliners (38.7%) were observed (Fig. 1A). Slow decliners included a subset of Aβ+ MCI participants with favorable baseline ADAS-Cog-13 scores and prognosis, while fast decliners showed a more impaired baseline status and a rapidly progressing longitudinal cognitive decline. The baseline values of the three trajectory subgroups were 7.96 (slow decliners), 14.23 (intermediate decliners), and 21.88 (fast decliners) (Supplementary Table 1). The values of the three trajectory subgroups increased from baseline at the 5-year follow-up, and the change showed stable, intermediate, and fast patterns. In fact, the change in cognitive decline of slow decliners was -1.66 points after 3 years and 0.84 points after 5 years. On the other hand, the change in cognitive decline of intermediate and fast decliners was 1.91 and 10.35 points after 3 years and 6.85 and 19.64 points after 5 years, respectively. Therefore, the difference between the trajectory subgroup in cognitive decline did not increase linearly (Fig. 1).

Similarly, in the internal validation analysis, the training and testing sets displayed three distinguishable trajectories, and model 6 showed quadratic, quadratic, and linear shapes of trajectories, respectively. The ΔBIC of model 6 compared with other models was between 6 and 10 in the training set, so it could be said that there was strong evidence against other models for model selection. In the testing set, model 6 showed the better fit, but there was little difference in the BIC with model 5. Therefore, we could confirm the three trajectory subgroups with quadratic, quadratic, and linear trajectory patterns (model 6) (Supplementary Table 3).

The same trajectory subgroups and similar trajectory shapes were identified in the Aβ- MCI participants of the ADNI. In the Aβ- and Aβ+ MCI participants, the change in cognitive decline of fast decliners was 3.53 and 10.35 points after 3 years, and 5.88 and 19.64

points after 5 years, respectively (Supplementary Table 1). The proportions of slow and fast decliners in the Aβ- and Aβ+ MCI groups were different. Specifically, fast decliners were more frequent in the Aβ+ (38.7%) than in the Aβ- (16.5%) group. On the other hand, slow decliners were more frequent in the Aβ- (36.3%) than in the Aβ+ (18.5%) group (Fig. 1A, 1B).

In addition, we also performed GBTM using the longitudinal CDR-SOB scores in the Aβ+ and Aβ- MCI groups (Fig. 2A, 2B). Briefly, the frequencies of fast, intermediate, and slow decliners were 14.3%, 29.8%, and 55.9% in the Aβ+ group and 2.8%, 23.1%, and 74.2% in the Aβ- group.

The same trajectory subgroups were also identified in Aβ+ MCI participants of the SMC (Fig. 2C). The frequencies of fast, intermediate, and slow decliners (60.32%, 27.0%, and 12.7%, respectively) was similar to those from the ADNI.

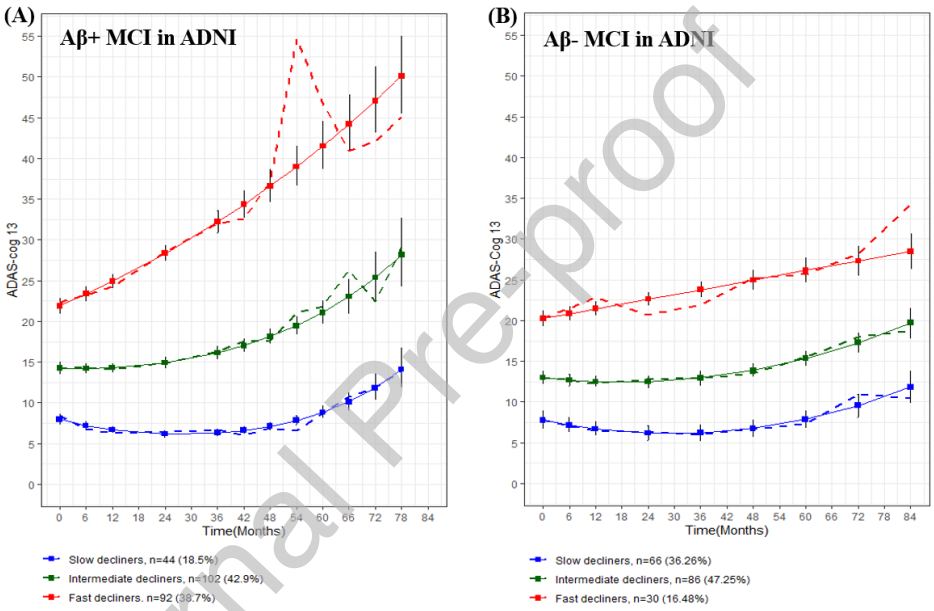

Fig. 1. The longitudinal trajectories of cognitive decline of (A) Aβ+ MCI participants and (B) Aβ- MCI participants over time according to the ADAS-Cog-13 score. The y-axis represents the Alzheimer's Disease Assessment Scale-cognitive subscale 13 (ADAS-Cog-13) scores. Three trajectory subgroups were identified: slow, intermediate, and fast decliners. Dashed lines and solid lines indicate the mean of the observed trajectories and the estimated trajectories, respectively.

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; Aβ+, amyloid beta-positive; Aβ-, amyloid beta-negative; MCI, mild cognitive impairment.

Table 2 The BIC values, SABIC values and average posterior probabilities of the group-based trajectory models

	Number of trajectory subgroups	Trajectory shapes†	BIC		SABIC		Average posterior probability for each trajectory	Selecting the Best model				
			n=1286‡	n=238§	n=1286‡	n=238§		Model comparison	ΔBIC (n=1286)‡	ΔBIC (n=238)§	ΔSABIC (n=1286)‡	ΔSABIC (n=238)§
Model 1	1	2	1961.3	1954.5	1964.5	1951.0	100.0	-				
Model 2	2	1, 1	1219.1	1210.7	1215.2	1201.7	98.3, 98.9	model 2 vs 1	742.2	743.8	749.3	749.3
Model 3	2	2, 1	1204.1	1194.0	1196.8	1181.7	98.6, 98.6	model 3 vs 2	15.0	16.7	18.3	20.0
Model 4	3	1, 1, 1	885.0	873.2	870.8	855.6	98.8, 92.6, 96.6	model 4 vs 3	319.1	320.8	326.1	326.1
Model 5	3	2, 1, 1	847.0	833.5	829.5	812.7	98.2, 93.3, 96.9	model 5 vs 4	38.0	39.7	41.2	42.9
Model 6	3	2, 2, 1	840.9	825.7	820.3	801.8	98.5, 93.6, 96.3	model 6 vs 5	6.1	7.8	9.3	11.0
Model 7	3	2, 2, 2	862.3	842.1	824.2	804.1	98.6, 93.6, 96.3	model 7 vs 6	-21.4	-16.4	-4.0	-2.3

The difference Δ in the BIC (SABIC) indicates that the best models are either a model (k-1) and a model k (k=2, 3 …,7).

Abbreviations: BIC, Bayesian information criterion; SABIC, sample size-adjusted Bayesian information criterion.

† Trajectory shapes: 1=linear, 2: quadratic; ‡ Total number of observations; § Total number of participants

Table 3 Parameter comparisons for the trajectory subgroups between the original and the bootstrap samples

Group	Parameter	Original sample	Bootstrap sample	delta of beta† (95% CI)
		Beta (SE)	Beta (SE)	
Slow decliners	Intercept	2.3 (0.03)	2.29 (0.01)	0.007 (-0.063-0.076)
	Linear	-0.01 (0.003)	-0.01 (0.0004)	0.000316 (-0.005-0.005)
	Quadratic	0.0003 (0.00004)	0.0003 (0.000008)	0 (-0.00008-0.000079)
Intermediate decliners	Intercept	2.79 (0.02)	2.78 (0.004)	0.003 (-0.045-0.05)
	Linear	-0.001 (0.002)	-0.001 (0.0002)	0 (-0.004-0.004)
	Quadratic	0.0001 (0.00003)	0.0001 (0.000002)	0 (-0.00005-0.00006)
Fast decliners	Intercept	3.17 (0.02)	3.17 (0.003)	0.001 (-0.039-0.042)
	Linear	0.01 (0.001)	0.01 (0.0001)	0 (-0.00142-0.00147)

Abbreviations: CI, confidence interval; SE, standard error.

†Reported as the difference in the estimated parameters between the original and bootstrap samples

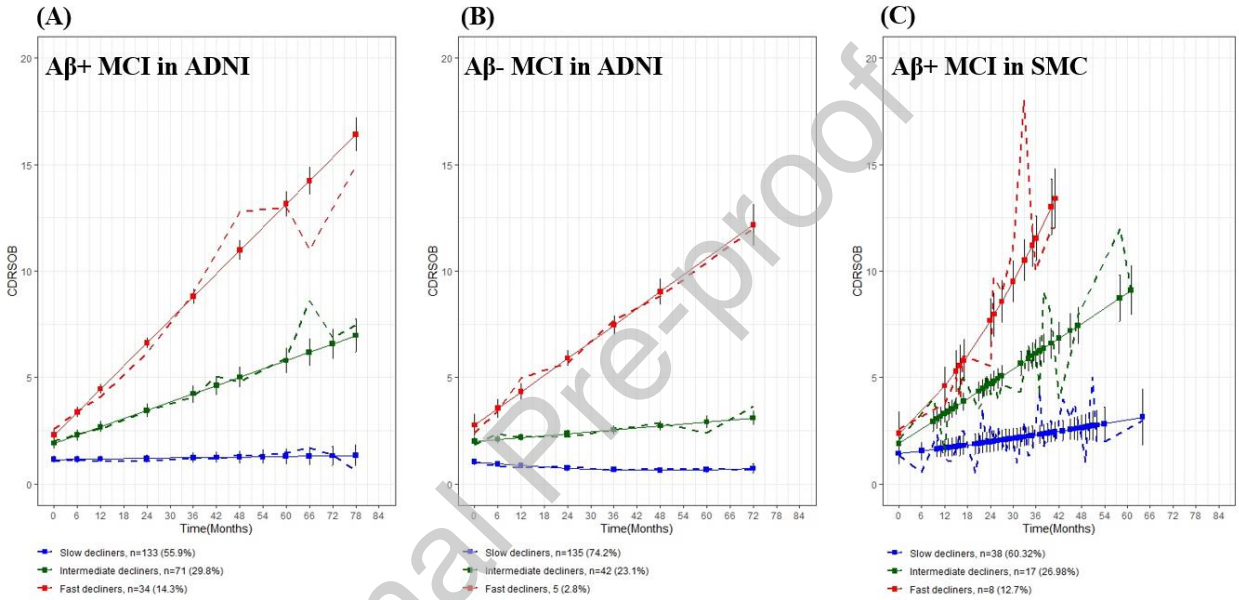

Fig. 2. The longitudinal trajectories of cognitive decline of (A) Aβ+ MCI participants in ADNI (B) Aβ- MCI participants in ADNI and (C) Aβ+ MCI participants in SMC over time according to the CDR-SOB score. Three trajectory subgroups were identified: slow, intermediate, and fast decliners. Dashed lines and solid lines indicate the mean of the observed trajectories and the estimated trajectories, respectively.

Abbreviations: Aβ+, amyloid beta-positive; Aβ-, amyloid beta-negative; CDR-SOB, Clinical Dementia Rating-Sum of Boxes scores; MCI, mild cognitive impairment; ADNI, Alzheimer's Disease Neuroimaging Initiative; SMC, Samsung Medical Center

3.3. Comparison of the clinical characteristics of the trajectory subgroups

Table 4 shows the significant baseline predictive demographic variables and biomarkers for identifying individuals who are at risk for fast decline. The median age was the lowest in the slow decliner (Tukey's test using ranks: slow vs. intermediate $p<0.001$; slow vs. fast $p=0.001$; intermediate vs. fast $p=0.692$). The gender composition did not significantly differ (Chi-square test; $p=0.483$) among three subgroups, but the duration of education was higher in the slow decliners than in intermediate decliners (Tukey's test using ranks: slow vs. intermediate $p=0.022$; slow vs. fast $p=0.321$; intermediate vs. fast $p=0.289$). The presence of *APOE ε4* was more frequent among fast decliners than slow and intermediate decliners (Fisher's exact test with permutation method for multiple testing: slow vs. intermediate $p=0.828$; slow vs. fast $p=0.003$; intermediate vs. fast $p=0.003$). In regards to biomarkers, all the analyzed markers significantly differed among the three decliner types. The median AV45 PET SUVR was lower in the slow decliners than in the other two subgroups (Tukey's test using ranks: slow vs. intermediate $p<0.001$; slow vs. fast $p<0.001$; intermediate vs. fast $p=0.003$). In addition, the median FDG PET SUVR was lower in the fast decliners than in the other two decliners (Tukey's test using ranks: slow vs. intermediate $p=0.001$; slow vs. fast $p<0.001$; intermediate vs. fast $p<0.001$).

Table 4 Demographics and clinical characteristics of the three trajectory subgroups

	Slow decliners (n=44)	Intermediate decliners (n=102)	Fast decliners (n=92)	p-value †	Slow vs. Intermediate p-value	Slow vs. Fast p-value	Intermediate vs. Fast p-value
Demographics							
Age, median (IQR), years	68.4 (65.3-72.5)	75.2 (68.9-79.3)	74.0 (69.7-77.5)	<0.001[a]	<0.001[c]	0.001[c]	0.692[c]
Age ≥70 years, N (%)	17 (38.64)	70 (69.31)	68 (73.91)	<0.001[b]	0.002[d]	<0.001[d]	0.729[d]
Female sex, N (%)	23 (52.27)	43 (42.16)	39 (42.39)	0.483[b]	0.503[d]	0.56[d]	1[d]
Education, median (IQR), years	17 (16-19.5)	16 (13-18)	16 (14-18)	0.027[a]	0.022[c]	0.321[c]	0.289[c]
Education >12 years, N (%)	41 (93.2)	79 (78.2)	76 (82.6)	0.091[b]	0.059[d]	0.2[d]	0.69[d]
Biomarkers							
APOE ε4 carriers, N (%)	24 (54.55)	62 (60.78)	75 (81.52)	0.001[b]	0.828[d]	0.003[d]	0.003[d]
AV45 PET SUVR, median (IQR)	1.2 (1.2-1.3)	1.4 (1.2-1.5)	1.4 (1.3-1.5)	<0.001[a]	<0.001[c]	<0.001[c]	0.003[c]
FDG PET SUVR, median (IQR)	1.4 (1.3-1.4)	1.3 (1.2-1.3)	1.2 (1.1-1.2)	<0.001[a]	0.001[c]	<0.001[c]	<0.001[c]

Abbreviations: APOE, apolipoprotein E; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose; PET, positron emission tomography; IQR, interquartile range

† Overall comparison of the three trajectory subgroups; a: Kruskal-Wallis test; b: Chi-square test; c: Tukey test using ranks; d: Fisher's exact test with permutation method for multiple testing

3.4. Development of the prediction model

Table 5 shows the fitness and predictability indices of the models, as well as the results of the goodness-of-fit comparison tests. Model 5, which considered age, *APOE ε4* genotype status, FDG SUVR, AV45 SUVR, and duration of education, and model 6, which excluded duration of education yielded a lower AIC and SC, as well as higher R-square, M-index, and PDI values, indicating that these two models were superior to the others. Models 5 and 6 exhibited similar fitness performances and predictability, with no significant differences in terms of goodness-of-fit (LRT; p=0.183). However, model 6 was selected as the final model due to the relatively lower number of predictive factors that it included. In model 6, intermediate decliners were associated with advanced age (≥70 years) (OR 2.72, 95% CI 1.78-6.28), a higher AV45 SUVR (OR 1.69, 95% CI 1.22-2.34), and a lower FDG SUVR (OR 0.65, 95% CI 0.46-0.93), but not a higher proportion of *APOE ε4* carriers (OR 1.53, 95% CI 0.66, 3.54) than slow decliners. Fast decliners were associated with advanced age (≥70 years) (OR 3.76, 95% CI 1.40-10.10), a higher proportion of *APOE ε4* carriers (OR 4.2, 95% CI 1.53-11.58), a higher AV45 SUVR (OR 2.14, 95% CI 1.50-3.05), and a lower FDG SUVR (OR 0.31, 95% CI 0.20-0.48) than slow decliners (Table 6).

Similar prediction models were also developed for Aβ+ MCI participants of the SMC (Supplementary Table 2). Model 6 showed the best predictive performance and fitness compared to other models.

3.5. Visualization of the prediction model

Finally, we visualized the risk scores and the predicted probability of belonging to a trajectory subgroup using the prediction model given the values of the participant's predictors

(Fig. 3). Specifically, for a participant aged 75 years, *APOE ε4* carrier, an AV45 SUVR of 1.3, and an FDG SUVR of 1.2, the risk scores of all predictors, as well as the intercept value, were higher in the fast decliners than in the intermediate decliners. Therefore, the linear predictor was also higher (2.05 vs 1.92; Fig 3A, 3B), so the probability of belonging to fast decliners was estimated to be higher than the probability of belonging to intermediate decliners (50.0% vs 43.6%; Fig 3A, 3B). The predicted probability of being in slow decliners was 6.4% (=100% – [43.6% + 50%]).

Table 5 Comparisons of models that include different combinations of predictors

	AIC	SC	R-Square	M-index	95% CI for M-index (Using 1,000 bootstrap samples)		PDI	Likelihood ratio test			
					Lower	Upper		Model comparison	Chi-squared statistic	DF	p-value
Model 1	485.47	506.28	0.10	0.63	0.57	0.68	0.27	-	-	-	-
Model 2	472.00	499.75	0.17	0.67	0.6	0.72	0.43	Model 1 vs. Model 2	17.47	2	0.0002
Model 3	416.76	451.44	0.39	0.78	0.72	0.83	0.66	Model 2 vs. Model 3	59.25	2	<0.0001
Model 4	439.59	474.27	0.31	0.75	0.65	0.78	0.61	Model 2 vs. Model 4	36.41	2	<0.0001
Model 5	398.74	440.36	0.45	0.81	0.74	0.85	0.70	Model 3 vs. Model 5	22.01	2	<0.0001
								Model 4 vs. Model 5	44.84	2	<0.0001
Model 6	398.16	432.84	0.44	0.81	0.73	0.85	0.69	Model 5 vs. Model 6	3.41	2	0.1813

Model 1: age, education

Model 2: age, education, *APOE ε4* (carrier, non-carrier)

Model 3: age, education, *APOE ε4*, FDG PET SUVR

Model 4: age, education, *APOE ε4*, AV45 PET SUVR

Model 5: age, education, *APOE ε4*, FDG PET SUVR, AV45 PET SUVR

Model 6: age, *APOE ε4*, FDG PET SUVR, AV45 PET SUVR

Abbreviations: CI, confidence level; APOE, apolipoprotein E; PET, positron emission tomography; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose; AIC, Akaike information criterion; SC, Schwarz criterion; M-index, Multiclass area under receiver operating characteristic index; PDI, polytomous discrimination index; DF, degrees of freedom

Table 6 Multinominal logistic regression for predictors of the Aβ+ MCI trajectory subgroup

	Intermediate decliners †			Fast decliners †		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, (≥70 years)	2.72	1.78, 6.28	0.002	3.76	1.40, 10.10	<0.001
Presence of *APOE ε4*	1.53	0.66, 3.54	0.158	4.20	1.53, 11.58	<0.001
AV45 PET SUVR‡	1.69	1.22, 2.34	<0.001	2.14	1.50, 3.05	<0.001
FDG PET SUVR‡	0.65	0.46, 0.93	<0.001	0.31	0.20, 0.48	<0.001

Abbreviations: Aβ+, amyloid beta-positive; MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval; APOE, apolipoprotein E; PET, positron emission tomography; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose. † Slow decliners as reference; ‡ Multiplied by ten

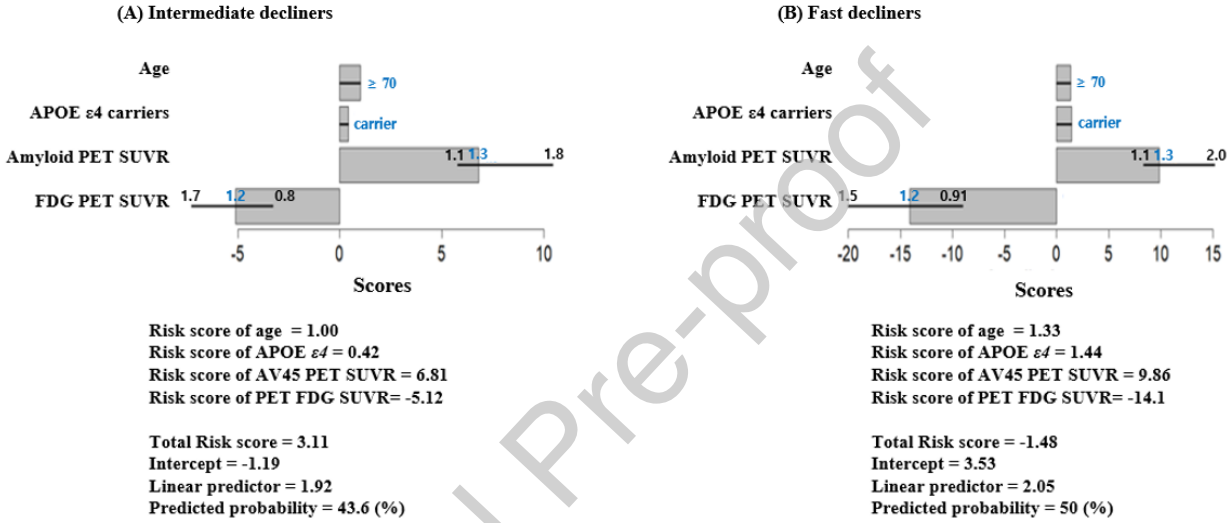

Fig. 3. Graphical representation of the predictive model. The case is that of a 75-year-old patient carrying the *APOE ε4* allele, with an AV45 SUVR of 1.3, and a FDG SUVR of 1.2. (A) Risk scores, linear predictor and predicted probability of intermediate decliners (B) Risk scores, linear predictor and predicted probability of fast decliners. The black lines indicate the range of the risk score for each predictor as observed in the dataset. The gray box indicates the predictors' risk scores for the patient. The specific predictor values given to the patient are indicated in blue color. All the predictors' risk scores were added to the model's intercept value to obtain a linear predictor. (A) represents the linear predictor for intermediate decliners compared with slow decliners, wherein the predicted probability corresponds to intermediate decliners. The predicted probability of the linear predictor is 43.6%. (B) represents the linear predictor for fast decliners compared to slow decliners, wherein the predicted probability corresponds to fast decliners. The predicted probability of the linear predictor is 50%. The predicted probability for slow decliners is 6.4% (=100% - (43.6%+50%)).

Abbreviations: APOE, apolipoprotein E; PET, positron emission tomography; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucos

4. Discussion

In the present study, we investigated several trajectories based on longitudinal cognitive decline through the ADAS-Cog-13 scores of participants with MCI due to AD. Our main findings were as follows: 1) three subgroups were identified: slow, intermediate, and fast decliners; 2) age ≥70 years, the presence of the *APOE ε4* allele, high amyloid SUVR, and hypometabolism were predictive of fast decline; 3) our newly developed prediction model serves to estimate the probability of belonging to each subgroup according to the presence of the above-mentioned predictive factors.

Our first major finding was that participants with Aβ+ MCI can be classified into three subgroups (slow, intermediate, and fast decliners) based on changes in their cognitive performance. As we expected, Aβ+ MCI participants show more rapid progression than Aβ- MCI participants, a result that is consistent with our previous findings indicating that Aβ+ MCI individuals have a higher risk of dementia progression compared to Aβ- MCI individuals (Ye et al., 2018). The results of the external validation analysis also showed similar patterns to the data obtained from the ADNI dataset. These results are in line with previous studies showing that individuals with MCI, regardless of the presence or absence of amyloid, have distinguishable trajectories of cognitive decline (Bhagwat et al., 2018). However, unlike previous studies, our research focused on individuals with Aβ+ MCI because most clinical trials have been recruiting this patient population. In particular, our modeling approach extends beyond the recent binary classifications created through discretionary criteria regarding the progression from MCI to dementia within a three-year period. Furthermore, our study employed a data-driven classification of Aβ+ MCI based on longitudinal cognitive performance rather than on *a priori* classifications.

Similarly, utilizing the CDR-SOB scores as a measurement of cognitive trajectory, three different trajectories were distinguishable in both the Aβ+ and Aβ- MCI groups as well. However, slow decliners seemed to be stable, and the frequency of fast decliners was lower than that obtained using the ADAS-Cog-13 scores. The frequency of fast decliners in Aβ- MCI participants (2.8%) was still lower than in Aβ+ MCI participants (14.3%) using CDR-SOB. These differences might be explained by the fact that the CDR-SOB (range: 0-17) has less variation than the ADAS-Cog-13 scale (range: 0-85).

Since the GBTM assumes that individuals within each trajectory subgroup started at the same value (zero variance around the intercept) and expressed the same pattern over time (zero variance around the slope), all individuals assigned to a trajectory have identical intercepts and slopes. This simplifies the explanatory aspect of the model because, in the absence of any intragroup variance, it could be sufficient to solely explain trajectory membership (Frankfurt et al., 2016). The Latent Class Growth Model (LCGM) and Growth Curve Model (GCM) were also applied to the to Aβ+ MCI data, but neither of these models converge due to negative variance in the Aβ+ MCI dataset. In fact, like in other research regarding trajectory data of cognitive aging and MCI (Ding et al., 2019; Koscik et al., 2020), the GBTM (Nagin and Odgers, 2010) was best suited to identify distinguishable trajectories.

Our second major finding was that advanced age, the presence of the *APOE ε4* allele, a high amyloid SUVR, and hypometabolism were predictive of a fast decline, a finding that is consistent with previous studies showing that advanced age and hypometabolism are predictive of faster disease progression in patients with MCI (Jang et al., 2019; Landau et al., 2012). A notable finding was that greater Aβ deposition predicted a faster decline in Aβ+ MCI patients. Several studies have demonstrated that Aβ deposition is reflective of early changes in AD (van Rossum et al., 2012). However, there are some debates regarding the

association of Aβ with disease stage, disease severity, and rate of cognitive decline (Hansson et al., 2006; Ingelsson et al., 2004; Jack et al., 2010). In fact, in the present study, when adding Aβ-related quantitative information to the prediction model, the R-square value increased from 0.39 (model 3) to 0.45 (model 5). Therefore, our finding seems to support that higher Aβ deposition is predictive of a more severe AD status. Another notable finding was that Aβ+ MCI participants carrying the *APOE ε4* allele displayed a rapid cognitive decline that is more frequent that that of non-carriers and independent from of Aβ deposition levels and downstream markers. *APOE ε4* is the most relevant genetic risk factor for AD and has been consistently associated with abnormal Aβ aggregation and deposition (Liu et al., 2013). However, our findings suggest that *APOE ε4* may influence not only cognitive decline via unknown underlying mechanisms but also Aβ and other downstream mechanisms in Aβ+ MCI individuals.

Despite that model 6 showed the highest prediction accuracy, the predictive factors added to this model may not be available in each clinical setting. For example, models 1 or 2, which consist of basic demographic variables and genotype data, might be more helpful in primary memory clinics. Similarly, models 3, 4, 5 or 6, which include brain imaging factors, could be exclusively used in tertiary hospitals where brain scans can be performed.

The final major contribution of this study is the introduction of a model that can serve to predict and visualize the individual risk of developing AD dementia even in a relatively homogenous patient population with Aβ+ MCI. In the present study, we have visualized, for each predictor, both the risk and total scores to assess the predicted probability of belonging to a trajectory subgroup considering the set of predictors of an individual patient. Therefore, our model may easily obtain clinically valuable results while also allowing for a more intuitive interpretation of the results.

This study has several limitations. Firstly, serial magnetic resonance imaging (MRI) factors such as brain structural volume, as well as the potential presence of underlying diseases, including vascular risk factors, were not included. Secondly, to assess Aβ positivity, we used a quantitative SUVR cut-off rather than a visual interpretation. However, although visual assessment can be more easily used in clinical settings, the SUVR cut-off is more sensitive for predicting the probability of the risk of decline. Despite these limitations, our novel prediction model highlights the clinical utility and applicability of risk prediction for disease progression.

5. Conclusions

In summary, our analysis provides novel insights into the different cognitive trajectories among patients with Aβ+ MCI. The prediction model that was developed in this study could facilitate the classification of patients with Aβ+ MCI, which could be employed in future clinical trials researching the role of Aβ deposition in AD.

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Disclosure of conflicts of interests

The authors declare that they have no competing interest.

Author contributions

SK and SWS designed the study, in collaboration with all other co-authors. SJK and SYW were responsible for data acquisition and analysis, as well as for the drafting of the manuscript. YJK and HJ contributed to data collection. SK and SYW were the responsible statistician and conducted the analyses. SK and SWS contributed to the hypothesis, interpretation of the data, and manuscript revision. All authors read and approved the final version of the manuscript.

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