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RESEARCH ARTICLE

Predicting cognitive stage transition using p-tau181, Centiloid, and other measures

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Abstract

BACKGROUND: A combination of plasma phospho-tau (p-tau), amyloid beta (Aβ)-positron emission tomography (PET), brain magnetic resonance imaging, cognitive function tests, and other biomarkers might predict future cognitive decline. This study aimed to investigate the efficacy of combining these biomarkers in predicting future cognitive stage transitions within 3 years.

METHODS: Among the participants in the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE-V) study, 49 mild cognitive impairment (MCI) and 113 cognitively unimpaired (CU) participants with Aβ-PET and brain imaging data were analyzed.

RESULTS: Older age, increased plasma p-tau181, Aβ-PET positivity, and decreased semantic fluency were independently associated with cognitive stage transitions. Combining age, p-tau181, the Centiloid scale, semantic fluency, and hippocampal vol-

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ume produced high predictive value in predicting future cognitive stage transition (area under the curve = 0.879).

CONCLUSIONS: Plasma p-tau181 and Centiloid scale alone or in combination with other biomarkers, might predict future cognitive stage transition in non-dementia patients.

KEYWORDS
Alzheimer's disease, Centiloid, cognitive stage, prognosis, p-tau

Highlights

- Plasma p-tau181 and Centiloid scale might predict future cognitive stage transition.
- Combining them or adding other biomarkers increased the predictive value.
- Factors that independently associated with cognitive stage transition were demonstrated.

1 | BACKGROUND

Discriminating individuals who are likely to show cognitive decline in the near future among patients without dementia, including cognitively unimpaired (CU) and mild cognitive impairment (MCI) patients, remains challenging for clinicians.[1] Early diagnosis, initiation of appropriate symptomatic treatment, and future planning are important not only for clinicians but also for patients and their caregivers. Administration of disease-modifying drugs, some of which are in use and others are in development, further increases this importance.[2]

Alzheimer's disease (AD) is characterized by the accumulation of amyloid beta (Aβ), aggregation of hyperphosphorylated tau, and neuronal loss.[3] These pathologic findings are initiated several years prior to cognitive decline. Considering these findings, the usefulness of diverse AD biomarkers for progression to AD dementia (ADD), such as brain magnetic resonance imaging (MRI) findings, Aβ-positron emission tomography (PET) positivity, cerebrospinal fluid analysis, and blood-based biomarkers in the early stages of AD have been reported previously.[1,3–7]

Among blood-based biomarkers, plasma phospho-tau (p-tau) 181, 217, and 231 showed high performance in discriminating AD and non-AD individuals.[6] Plasma p-tau was associated with progression to ADD in CU and MCI participants.[1,8] Aβ-PET positivity, usually analyzed with standard uptake volume ratios (SUVRs), is also known to increase the risk of cognitive decline in CU and MCI participants.[4,9] Recently, measures from different Aβ tracers (florbetapir, florbetaben, and flutemetamol) were standardized into a scale called Centiloid.[10] The Centiloid scale was also associated with greater risk of disease progression in patients without dementia.[11] However, combining plasma p-tau and Aβ-PET results to predict future cognitive decline in patients without dementia was not investigated previously.

The current study aimed to demonstrate the efficacy of plasma p-tau181, Centiloid, and other accessible measures for predicting cognitive stage transition in patients without dementia over a 3-year period using the data from the Korea Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE-V) cohort. Among the diverse biomarkers (including brain MRI, Aβ-PET, plasma p-tau181, and cognitive function test), we attempted to identify independent predictors for future cognitive stage transition. In addition, the correlation between plasma p-tau181 and Centiloid was analyzed. Finally, considering the multifactorial nature of AD, other measures were combined with plasma p-tau181 and Aβ status (Centiloid) to establish the best fit, easily available, non-invasive model for predicting cognitive stage transition within 3 years among CU and MCI participants.

2 | METHODS

2.1 | Participants

This study analyzed data from an independent validation cohort of the KBASE-V.[3,12] The KBASE-V contains a nationwide cohort, including CU, MCI, and ADD participants, from nine hospitals across South Korea from April 2015 to August 2016. The participants were aged between 55 and 90 y. Among these participants, the eligible patients for the current study were those with (1) CU or MCI and (2) Aβ-PET data. In total, 113 CU and 49 MCI participants were included in this study.

All CU participants had a normal (≥1.5 standard deviations [SDs] below the age-, sex-, and education-adjusted normative means) performance on four memory tests of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; semantic fluency, naming test, word list immediate recall, constructional praxis, word list delayed recall, word list recognition, and constructional praxis recall) and a global Clinical Dementia Rating (CDR) scale score of 0.[13–15] MCI participants met the core clinical criteria for MCI due to AD established by the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups[16], and the following criteria were modified

from those proposed by Petersen et al.[17]: (1) CDR scale score of 0.5; (2) memory complaints by patients, caregivers, or clinicians; (3) a performance score < 1.5 SDs below the age-, education-, and sex-adjusted normative means for one or more of the four memory tests included in the CERAD; (4) the ability to perform independent activities of daily living (ADL)[18]; and (5) absence of dementia. All participants had a reliable informant who could provide requested information to the investigators. The exclusion criteria were as follows: (1) presence of major psychiatric illness; (2) significant neurological or medical conditions or comorbidities that could affect cognitive function; (3) contraindications for MRI (e.g., pacemaker and claustrophobia); (4) illiteracy; (5) severe visual or hearing difficulty or serious communication or behavioral problems that could hinder clinical examination or brain imaging; (6) receiving an investigational drug; and (7) pregnancy or breastfeeding.[12]

2.2 | Clinical assessment

All participants underwent yearly physical and neurological examinations, including thorough diagnostic procedures that assessed their cognition, abnormal behaviors, ADL, demographic characteristics, family history, current medications, vascular risk factors (the presence of hypertension, diabetes, and dyslipidemia, as well as smoking status), and other comorbidities using the Mini-Mental State Examination (MMSE)[13], Geriatric Depression Scale[19], Blessed Dementia Scale-ADL[20], CDR scale, and CERAD.[12,21] The CERAD includes semantic fluency (animal category, J1), modified Korean version of the Boston Naming Test (J2), MMSE (J3), word list immediate recall (J4), constructional praxis (J5), word list delayed recall (J6), word list recognition (J7), and constructional recall (J8).[13] Each domain was converted to a z-score on the basis of the test score distribution in the present population.

Laboratory tests, including apolipoprotein E (APOE) genotyping, were performed at baseline. The APOE status was modeled as one variable coded for the presence of the $\varepsilon 4$ allele ($\varepsilon 4$ carrier or not). The participants' weight and height were measured while they were wearing light clothing. The participants' body mass index was calculated using their weight (kg) divided by the square of their height (m^2).

2.3 | Brain MRI

All participants underwent brain MRI. A 3.0-T MRI scanner was used to capture three-dimensional (3D) T1- and T2-weighted SPACE sagittal images with a 0.8-mm thickness. AD Neuroimaging Initiative phase 2 MRI protocols were used for brain MRI.[12,22] The 3D T1-weighted MRI parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 2.14 ms, inversion time (TI) = 900 ms, flip angle (FA) = 9°, and voxel resolution = 0.8 × 0.8 × 0.8 mm^3 in the Skyra and Trio Tim scanners (Siemens, Washington, DC, USA); TR = 7.32 ms, TE = 3.02 ms, TI = 400 ms, FA = 11°, and voxel resolution = 0.8 × 0.8 × 0.8 mm^3 in the General Electric Discovery MR750 scanner (GE Healthcare, Milwaukee, WI, USA); and TR = shortest (6.8 ms), TE = shortest (3.1 ms), FA = 9°, and voxel resolution = 0.8 × 0.8 × 0.8 mm^3 in the Achieva scanner (Philips Healthcare, Andover, MA, USA).

The measured MRI data were analyzed using CIVET pipeline version 2.1 (https://mcin.ca/technology/civet/).[23] The intensity difference from inhomogeneity in the magnetic field was calibrated using the N3 intensity nonuniformity correction algorithm, and the corrected T1-weighted images were aligned to the Montreal Neurological Institute 152 standard space.[24,25] The BET algorithm was adjusted to exclude non-brain tissue from the data.[26] The inner and outer surfaces of the cortex were estimated using a deformable spherical mesh and constrained Laplacian-based automated segmentation with proximities algorithm, respectively.[27] The cortical thickness values in the native space were obtained using the Euclidean distance between the linked vertices of the inner and outer surfaces.[28] The corrected T1-weighted images were segmented into the left and right sides of the hippocampus using FMRIB's integrated registration and segmentation tool.[29] The volumes of the hippocampus were normalized for the total intracranial volume.

2.4 | Amyloid PET

Amyloid pathological changes were considered positive when individuals had abnormal Aβ biomarkers based on cortical Aβ-PET ligand

RESEARCH IN CONTEXT

1. **Systematic Review**. The literatures in plasma phospho-tau (p-tau) and amyloid beta (Aβ)-positron emission tomography (PET) blood-based biomarkers for future cognitive decline were reviewed. Previous reports suggested that p-tau and Aβ-PET might predict future cognitive decline. However, there were no studies on the combination of p-tau181 and Aβ-PET for future cognitive stage transition.
2. **Interpretation**: Within 3 years, older age, increased plasma p-tau, Aβ-PET positivity, and decreased semantic fluency were independently associated with cognitive stage. Combining age, p-tau181, the Centiloid scale, semantic fluency, and hippocampal volume produced high accuracy in predicting cognitive stage transition (area under the curve = 0.879). Plasma p-tau181 and Centiloid scale correlated each other significantly.
3. **Future Direction**: These findings support plasma p-tau181 and Centiloid scale alone or in combination with other biomarkers, might predict future cognitive stage transition in non-dementia patients. Replication in other studies with refinement of the preanalytical and analytical factors for p-tau and Aβ-PET is recommended.

binding.[30] All the participants underwent Aβ-PET at baseline. Sixty participants underwent ^{11}C-PiB PET, and 102 participants underwent ^{18}F-flutemetamol PET.

The PET methods for each tracer have been previously described.[12,21] The SUVR was obtained using the pons as the reference region on ^{18}F-flutemetamol PET and the cerebellar gray matter as the reference region on ^{11}C-PiB PET. Centiloid replication analysis was performed according to previous reports.[10,31] Based on a previous study, positive amyloid pathology by Aβ-PET was defined as a cutoff point of 10 Centiloid units.[31,32]

2.5 | Plasma sampling and analysis

Plasma p-tau181 levels were available for 134 participants. This was measured using the Simoa Human p-Tau181 Advantage V2 assay (Quanterix Corp, Boston, MA, USA, PN/103714). For a typical run setup, each sample and control was transferred into 96-well Quanterix plates for duplicate tests with on-board 4× dilution by the instrument. The detailed instructions can be found in the Simoa Guide (Quanterix). The assay was run on a Simoa HD-X instrument (Quanterix) using a two-step immunoassay. Furthermore, the target antibody-coated paramagnetic beads were combined with the sample and biotinylated detector antibodies in the same incubation period. Target molecules present in the sample were captured by antibody-coated beads and were simultaneously bound to the biotinylated antibody detector.

2.6 | Outcome

The main outcome was the cognitive stage transition (from CU to MCI or dementia and from MCI to dementia) during the 3-year study period. The diagnosis of MCI was based on the core clinical criteria for MCI established by the NIA-AA workgroups[16] and the criteria modified from those proposed by Petersen et al.[17], as mentioned earlier.[12,21] The diagnosis of dementia was based on the DSM-IV-TR criteria for dementia[33], and the diagnosis of probable ADD was based on the NIA-AA core clinical criteria.[34]

2.7 | Statistical analyses

Participants were initially divided into two groups depending on the presence of cognitive stage transition within 3 years. Pearson's chi-squared and Mann–Whitney U tests were used to compare the baseline demographics and clinical data. The efficacy of measures, including p-tau181 and Centiloid, to correctly identify individuals with cognitive stage transition was determined using logistic regression models and receiver operating characteristic (ROC) curve analysis. Adjusted variables in the logistic regression analysis were selected from the results of the univariate analysis with $p < 0.05$ and potential confounders based on biological mechanisms. The p-tau181 was strongly associated with Centiloid (Figure 1), and the z-scores of neuropsychological tests in CERAD (except constructional praxis) correlated significantly (Table S1 in supporting information). Adjusted variables were age, plasma p-tau181, positive amyloid pathology, hippocampal volume, baseline diagnosis, hyperlipidemia, semantic fluency, and word list delayed recall. The different combinations of variables were tested (Table S2 in supporting information), and the model with the lowest Akaike information criterion (AIC) was considered the best-fit model. AIC is a model performance metric that considers the trade-off between model fit and sparsity. While ROC and area under the curve (AUC) explain how well a model performs on the given set of data, the AIC rather explains how well a model performs on unseen data.[1,35] The next step was to find models with as few variables as possible that had a similar performance, defined as ΔAIC < 2, from the model with the lowest AIC. This model was considered the parsimonious model.[1] The significance of the AUC for the different ROC curves was compared using the DeLong method. Improvements in model fit were estimated using the AIC with a decrease of two or more in AIC indicating a better model fit.[36,37] Statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing) and IBM SPSS version 27.0 (IBM Corp. Armonk, NY). Two-sided p value < 0.05 was considered statistically significant.

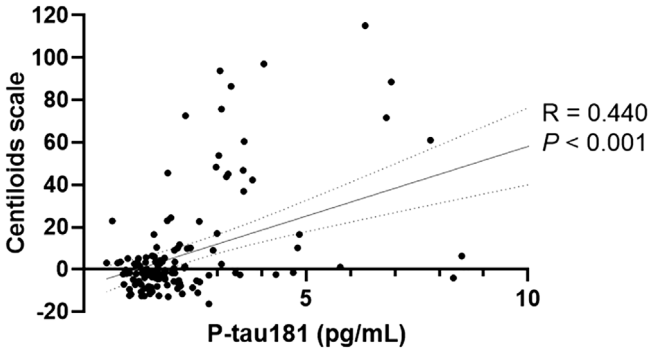

FIGURE 1 The correlation between the level of plasma p-tau181 and the Centiloid scale

3 | RESULTS

The current study analyzed 162 participants (113 CU and 49 MCI). The mean ± SD age was 68.8 ± 8.0 years (55-90 years), and 53.1% of participants were women. The follow-up period ranged from 12 to 49 months (mean ± SD: 33.1 ± 7.6 months). A total of 31 (19.1%) participants showed cognitive stage transition during the study period. The mean ± SD time to cognitive stage transition was 22.4 ± 9.5 months. Among the CU (n = 113) participants, 13 (11.5%) progressed to MCI and 2 (1.8%) progressed to dementia. Among the MCI (n = 49) participants, 16 (32.7%) progressed to dementia. Among a total of 162 participants, 35 (21.6%) had at least one APOE ε4 allele.

The clinical characteristics of the participants according to the cognitive stage transition are presented in Table 1. Compared with

TABLE 1 Clinical characteristics of participants based on cognitive stage transition over the 3-year study period.

	Non-converter ($n = 131$)	Converter ($n = 31$)	p-Value*
Demographics			
Age, years	67.2 ± 7.5	75.5 ± 6.5	<0.001*
Female	72 (55.0)	14 (45.2)	0.325
Lives alone	14 (10.7)	6 (19.4)	0.187
BMI, kg/m^2	24.5 ± 3.0	24.2 ± 2.4	0.539*
Education, years	10.5 ± 4.7	9.8 ± 5.2	0.481*
Baseline diagnosis			0.004
Cognitive unimpaired	98 (74.8)	15 (48.4)	
Mild cognitive impaired	33 (25.2)	16 (51.6)	
MMSE score, median (IQR)	27.0 (24.0–29.0)	23.0 (21.0–26.0)	<0.001[a]
CDR score, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.011[a]
CDR-SOB score, median (IQR)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	0.001[a]
Gdps score, median (IQR)	7.0 (4.0–12.0)	7110 (3.0–14.0)	0.139[a]
Semantic fluency, J1 (z-score)	0.165 ± 1.075	−0.534 ± 0.897	0.001*
Naming test, J2 (z-score)	0.630 ± 0.912	−0.032 ± 1.129	0.008*
Word list immediate recall, J4 (z-score)	0.347 ± 1.090	−0.438 ± 1.056	<0.001*
Constructional praxis, J5 (z-score)	0.071 ± 0.912	−0.010 ± 1.312	0.686*
Word list delayed recall, J6 (z-score)	−0.122 ± 1.063	−0.826 ± 1.094	0.001*
Word list recognition, J7 (z-score)	−0.742 ± 1.185	−0.924 ± 1.581	0.008*
Constructional praxis recall, J8 (z-score)	0.202 ± 1.004	−0.907 ± 0.866	<0.001*
Medical history			
Hypertension	57/129 (44.2)[b]	16 (51.6)	0.456
Diabetes mellitus	20 (15.3)	8 (25.8)	0.163
Hyperlipidemia	58/128 (45.3)[b]	7 (22.6)	0.021
Coronary artery disease	8 (6.1)	2 (6.5)	0.943**
Cerebrovascular disease	6 (4.6)	2 (6.5)	0.676**
Smoking	7 (5.3)	0 (0.0)	0.081**
Taking more than three pills	77 (58.8)	17 (54.8)	0.689
Hippocampal volume, cm^3	5.1 ± 0.8	4.3 ± 1.1	<0.001*
Cortical thickness, mm	3.10 ± 0.15	3.05 ± 0.13	0.104*
Positive amyloid pathology[b]	18 (13.8)	21 (67.7)	<0.001
Centiloid	2.93 ± 22.43	36.0 ± 36.9	<0.001*
APOE ε4 carrier	25 (19.1)	10 (32.3)	0.109
Plasma P-tau181 (pg/ml)	2.1 ± 1.3	3.6 ± 2.9	<0.001*

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; Gdps, Geriatric Depression Scale; IQR, interquartile range; MMSE, Mini-Mental State Examination.

Data are presented as means ± standard deviations or numbers (%) unless otherwise indicated.

p-value is based on the Pearson's chi-squared test, * Student's t-test, **Fisher's exact test, or [a]Mann–Whitney U test.

[b]Measured in partial cases in the non-converter group.

non-converters, converters were older, had lower MMSE, CDR, and CDR-SOB scores, memory, verbal, and executive functions, and hippocampal volume, and higher Centiloid and plasma p-tau181 levels. Hyperlipidemia was more frequent in non-converters.

The results of the multivariate logistic regression analysis are shown in Table 2. After adjusting for potential confounding variables, older age [odds ratio (OR) = 1.116; 95% confidence interval (CI) = 1.012–1.232; $p = 0.027$], plasma p-tau181 (OR = 1.355; CI = 1.015–1.809; $p = 0.040$), positive Aβ-PET (OR = 5.400; CI = 1.486–19.620; $p = 0.010$), and semantic fluency (per 0.1 z-score increase; OR = 0.927; CI = 0.866–0.993; $p = 0.027$) were independently associated with cognitive stage transition within 3 years.

TABLE 2 Multivariate logistic regression analysis of cognitive stage transition.

	Unadjusted OR	Adjusted OR model	*p*-Value
Age	1.170 (1.095–1.250)	1.117 (1.012–1.232)	0.027
Plasma p-tau181	1.459 (1.159–1.838)	1.355 (1.015–1.809)	0.040
Positive amyloid	13.067 (5.298–32.224)	5.400 (1.486–19.620)	0.010
Hippocampal volume, per 0.1 cm^3	0.905 (0.861–0.952)	0.934 (0.861–1.013)	0.098
Baseline diagnosis, MCI compared to CU	3.168 (1.413–7.102)	0.261 (0.049–1.386)	0.115
Hyperlipidemia	0.352 (0.142–0.875)	0.369 (0.095–1.437)	0.151
Semantic fluency, per 0.1 z-score increase	0.932 (0.892–0.974)	0.927 (0.866–0.991)	0.027
Word list delayed recall, per 0.1 z-score increase	0.942 (0.908–0.978)	0.971 (0.905–1.042)	0.415

Abbreviations: CU, cognitively unimpaired; MCI, mild cognitive impairment; OR, odds ratio.
Data are presented as odds ratios (95% confidence intervals).
p-Value for multivariate models.
Adjusted variables were selected from the results of the unadjusted univariate analysis with $p < 0.05$: age, plasma p-tau181, positive amyloid pathology, hippocampal volume, baseline diagnosis, hyperlipidemia, semantic fluency, and word list delayed recall.

In all participants, the best-fit model in terms of AIC was a model combining age, p-tau181, Centiloid, semantic fluency, and hippocampal volume (Table 3 and Table S2 in supporting information). Plasma p-tau181 (AUC = 0.673, CI: 0.539–0.806) and Centiloid (AUC = 0.759, CI: 0.647–0.871) alone showed moderate discriminative value in predicting cognitive stage transition (Table 3, Figure 2A). When combining age and plasma p-tau181, the discriminative value improved (AUC = 0.828, CI: 0.742–0.913), and this value was not significantly different from that of the best-fit model including age, p-tau181, Centiloid scale, semantic fluency, and hippocampal volume ($p = 0.0581$). Suggested threshold was 2.03 pg/ml for plasma p-tau181 (Table S3 in supporting information, sensitivity = 65.4, specificity = 64.8, positive predictive value [PPV] = 71.6, negative predictive value [NPV] = 93.3), and 9.0 for Centiloid (Table S4 in supporting information, sensitivity = 71.0, specificity = 84.0, PPV = 87.0, NPV = 94.4).

In CU participants, the best-fit model in terms of AIC was a model combining age, p-tau181, Centiloid scale, and semantic fluency with a high discriminative value in predicting cognitive stage (AUC = 0.811, CI: 0.690–0.932, Table 3, Figure 2B). The discriminative value was not significantly different when using a model combining age, p-tau181, and the Centiloid scale (AUC = 0.770, CI: 0.646–0.895, a parsimonious model) or a model combining age and p-tau181 (AUC = 0.760, CI: 0.640–0.811). The suggested threshold was 2.03 pg/ml for plasma p-tau181 (Table S5 in supporting information; sensitivity = 57.1, specificity = 67.1, PPV = 72.0, NPV = 93.5) and 2.52 for Centiloid (Table S6 in supporting information; sensitivity = 66.7, specificity = 71.4, PPV = 75.0, NPV = 95.5) in CU participants.

In MCI participants, the best-fit model in terms of AIC was a model combining age, p-tau181, and Centiloid with a very high discriminative value in predicting cognitive stage transition (AUC = 0.963, CI: 0.905–1.000, Table 3, Figure 2C). A parsimonious model included age and p-tau181 (AUC = 0.928, CI: 0.845–1.000). Plasma p-tau181 (AUC = 0.803, CI: 0.649–0.957) and Centiloid (AUC = 0.769, CI: 0.596–0.942) alone showed moderate to high discriminative value in predicting cognitive stage transition. The suggested threshold was 2.94 pg/ml for plasma p-tau181 (Table S7 in supporting information; sensitivity = 75.0, specificity = 86.2, PPV = 90.2, NPV = 92.7), and 30.0 for the Centiloid (Table S8 in supporting information; sensitivity = 75.0, specificity = 84.8, PPV = 96.9, NPV = 97.5) in MCI participants.

Additionally, the efficacy of p-tau181 and Centiloid in predicting cognitive stage transitions in different age groups was demonstrated (Table S9 in the supporting information). In the younger age group (age < 69 years, $n = 73$), the model combining age and p-tau181 showed a high discriminative value with the lowest AIC (AUC = 0.933, CI = 0.846–1.000). The model combining age and Centiloid also showed excellent discriminative value (AUC = 0.909, CI = 0.831–0.988).

4 | DISCUSSION

In this study, we showed that plasma p-tau181 (pg/ml) was significantly correlated with Centiloid (R = 0.440 and $p < 0.001$). Older age, increased plasma p-tau181, Aβ-PET positivity, and decreased semantic fluency were independently associated with cognitive stage transition within 3 years among CU and MCI patients. Plasma p-tau181 and Centiloid scale alone could predict cognitive stage transition accurately, especially in patients with MCI. In all participants, the best-fit model was when age, p-tau181, Centiloid, semantic fluency, and hippocampal volume were combined. Considering MCI participants only, the model combining age, p-tau181, and Centiloid showed the highest discriminative value in predicting cognitive stage transition within 3 years. The parsimonious model included only p-tau181 and age in CU and MCI patients.

This study is the first to demonstrate the efficacy of a model combining plasma p-tau181 and the results of Aβ-PET (Centiloid) in predicting future cognitive stage transition among patients without dementia. Other accessible biomarkers such as diverse cognitive function tests, brain MRI findings (hippocampal volume and cortical thickness), demographics, and comorbidities were considered to find the best-fit model to predict future cognitive stage transition. This model includes all amyloid (A), tau (T), and neurodegeneration (N) biomarkers consisting of

TABLE 3 Associations with disease conversion and biomarkers.

		Total			CU			MCI	
Model	AUC (95% CI)	AIC (ΔAIC) versus full model	*p-Value versus full model (*vs. *2)	AUC (95% CI)	AIC (ΔAIC) versus full model	*p-Value versus full model (*vs. *2)	AUC (95% CI)	AIC (ΔAIC) versus full model	*p-Value versus full model (*vs. *2)
1. Age, p-tau181, Centiloid, semantic fluency, hippocampal volume (full model)	0.879 (0.799–0.959)	95.7a (ref)	ref	0.826 (0.700–0.953)	70.8 (ref)	ref	0.961 (0.905–1.000)	28.9 (ref)	Ref
2. Age, p-tau181, Centiloid, semantic fluency	0.867 (0.786–0.948)	96.4b (0.7)	0.429 (NA)	0.811 (0.690–0.932)	70.8a (0.0)	0.499 (NA)	0.960 (0.906–1.000)	27.8 (−1.1)	0.689 (NA)
3. Age, p-tau181, Centiloid	0.846 (0.762–0.930)	100.2 (4.5)	0.130 (0.156)	0.770 (0.646–0.895)	74.0 (3.6)	0.226 (0.187)	0.963 (0.905–1.000)	27.7a (−1.2)	1.000 (0.858)
4. Age, Centiloid	0.852 (0.777–0.926)	117.1 (21.4)	0.127 (0.239)	0.770 (0.651–0.889)	80.3 (9.5)	0.181 (0.285)	0.911 (0.831–0.991)	40.3 (11.4)	0.295 (0.358)
5. Age, p-tau181	0.828 (0.742–0.913)	104.7 (9.0)	0.049 (0.0581)	0.760 (0.640–0.881)	72.7b (1.9)	0.173 (0.155)	0.928 (0.845–1.000)	30.2b (1.1)	0.233 (0.286)
6. P-tau181, Centiloid	0.745 (0.616–0.873)	112.8 (17.1)	0.009 (0.010)	0.643 (0.458–0.827)	79.2 (8.4)	0.007 (0.008)	0.822 (0.635–1.000)	35.9 (7.0)	0.075 (0.084)
7. Centiloid	0.759 (0.647–0.871)	133.4 (37.7)	0.017 (0.025)	0.723 (0.565–0.881)	84.9 (14.1)	0.083 (0.061)	0.769 (0.596–0.942)	50.6 (21.7)	0.096 (0.106)
8. P-tau181	0.673 (0.539–0.806)	117.2 (21.5)	<0.001 (< 0.001)	0.564 (0.369–0.760)	76.1 (5.3)	<0.001 (< 0.001)	0.803 (0.649–0.957)	40.4 (11.5)	0.022 (0.026)

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; CI, confidence interval; CU, cognitively unimparied; MCI, mild cognitive impairment; NA, not applicable; P-tau, phosphorylated tau.

Note: Results from logistic regression models with disease conversion as an outcome.

*p-Values are for comparisons of AUCs (using the DeLong test) to the full biomarker model.

[a] Best model fit; bparsimonious model.

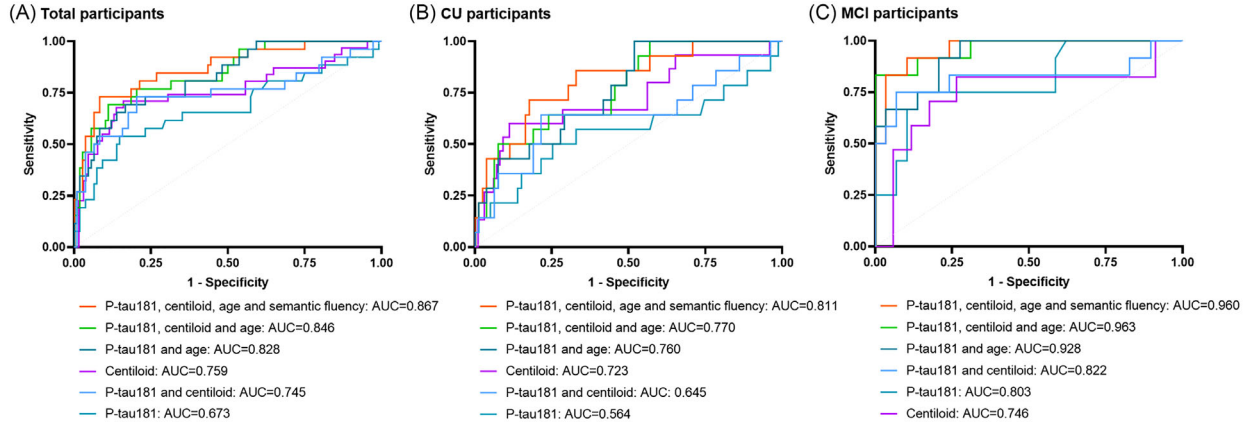

FIGURE 2 Receiver operating characteristic (ROC) curve analyses of the different models for discriminating those with cognitive stage transition in total (A), cognitive unimpaired (B), and mild cognitive impairment (C) patients. Among 162 patients, 31 show cognitive stage transition during 3 years and 134 have plasma p-tau181 data. AUC, area under curve

amyloid/tau/neurodegeneration (ATN) scheme based on the National Institute on Aging and Alzheimer's Association research framework.[30] The finding that plasma p-tau predicts future ADD in MCI participants is consistent with a previous report.[1] However, this previous study did not consider biomarkers for Aβ. Another strength is that the current study standardized diverse Aβ-PETs using different radiotracers into the Centiloid and analyzed Centiloid as a continuous variable. Previous reports showing an association between Aβ-PET signals and subsequent cognitive decline usually dichotomized participants into negative or positive Aβ status using SUVRs[4,9], which might reduce the explanatory information. In the current study, the Centiloid and plasma p-tau181 were considered as continuous variables and predicted future cognitive stage transition well.

Some previous studies have focused on evaluating the cutoff value on the Centiloid to discriminate AD.[31,32,38] These studies suggested that a Centiloid value of < 10-12 may discriminate the absence of amyloid plaque, and a Centiloid value of approximately 20-30 may reflect the presence of established amyloid pathology.[31,32] In our study, the cutoff value of Centiloid for predicting cognitive stage transition in MCI participants was 30.0 and that in CU participants was 2.5. According to our results, MCI participants with a Centiloid ≥30 were likely to convert to dementia within 3 years. CU participants with a Centiloid ≥2.5 are likely to show cognitive stage transition within 3 years. Centiloid values higher than 2.5 but less than 10 indicate the absence of amyloid pathology range according to previous reports.[31,32] However, even in these patients, caution is needed as they might have cognitive stage transition in the near future, even if they are not currently considered to have amyloid pathology. Accurately predicting the possibility of future cognitive stage transition by adding other accessible biomarkers in these patients would be valuable.

There has been repeated debates over the Aβ hypothesis.[39] In this study, Aβ-PET positivity was independently associated with cognitive stage transition after adjusting age, plasma p-tau181, hippocampal volume, baseline diagnosis, hyperlipidemia, semantic fluency, and memory function (word list delayed recall). To our knowledge, this study is the first to demonstrate a significant association between the Centiloid scale and plasma p-tau levels. These results support the Aβ hypothesis and that Aβ influences downstream processes, including tau phosphorylation, leading to neurodegeneration.[2,39] The finding that there is a close relationship between Aβ-PET status and plasma p-tau level is consistent with a previous study.[37] Although CSF or PET studies are accurate for detecting Aβ status, they are expensive or invasive. Further validation studies are needed to determine the efficacy of plasma p-tau as a noninvasive and cost-effective biomarker for discriminating patients who need or do not need CSF or PET studies.

This study had several limitations. First, only the baseline plasma p-tau181 and Aβ-PET status were analyzed. Analysis of longitudinal data will reveal more information and elucidate the usefulness of these biomarkers. Second, cross-validating our findings in other specialized cohorts, especially in the primary care population, is important, as the efficacy of the model including only plasma p-tau181 showed a moderate discriminative value in CU participants. However, the addition of other biomarkers to plasma p-tau181 significantly improved the discriminative value. Third, a single ethnic population (Koreans) with a relatively small number of participants, especially subjects with MCI, was enrolled and followed up for a short period (3 years). However, determining the possibility of cognitive stage transition is also meaningful, even though the number is relatively small and the period is a little short.

The development of a predictive model for future cognitive stage transition is expected to provide more accurate information for clinicians, patients, and caregivers. It can be useful for recruiting participants to AD clinical trials or motivate some individuals without dementia to receive disease-modifying drugs. If the improvement of plasma p-tau or Aβ-PET status is achieved after treatment, we expect this predictive model to allow clinicians to intuitively check the probability of the cognitive stage transition decreasing.

AUTHOR CONTRIBUTIONS

Hyuk Sung Kwon, Ji Young Kim, Seong-Ho Koh, and Seong Hye Choi made substantial contributions to the conception and design of the work. Hyuk Sung Kwon and Ji Young Kim drafted the manuscript. Seong

Hye Choi and Seong-Ho Koh revised the manuscript. All authors made substantial contributions to acquisition, analysis, or interpretation of data. Hyuk Sung Kwon made substantial contributions to statistical analysis. Eun-Hye Lee and Hyun-Hee Park made substantial contributions to administrative, technical, or material support. Jee Hyang Jeong, Jae-Won Jang, Kyung Won Park, Eun-Joo Kim, Jin Yong Hong, Soo Jin Yoon, Bora Yoon, and Myung Hoon Han supervised the study. All authors give final approval of the version published.

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CONFLICT OF INTEREST STATEMENT

Author disclosures are available in the supporting information.

DATA SHARING STATEMENT

The datasets used and analyzed during the current study are available from the corresponding authors upon reasonable request.

CONSENT STATEMENT

All of the participants provided written informed consent to participate in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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