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RESEARCH ARTICLE

Comparing machine learning-derived MRI-based and blood-based neurodegeneration biomarkers in predicting syndromal conversion in early AD

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Abstract

Introduction: We compared the machine learning-derived, MRI-based Alzheimer's disease (AD) resemblance atrophy index (AD-RAI) with plasma neurofilament light chain (NfL) level in predicting conversion of early AD among cognitively unimpaired (CU) and mild cognitive impairment (MCI) subjects.

Methods: We recruited participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) who had the following data: clinical features (age, gender, education, Montreal Cognitive Assessment [MoCA]), structural MRI, plasma biomarkers (p-tau$_{181}$, NfL), cerebrospinal fluid biomarkers (CSF) (Aβ42, p-tau$_{181}$), and apolipoprotein E (APOE) ε4 genotype. We defined AD using CSF Aβ42 (A+) and p-tau$_{181}$ (T+). We defined conversion (C+) if a subject progressed to the next syndromal stage within 4 years.

Results: Of 589 participants, 96 (16.3%) were A+T+C+. AD-RAI performed better than plasma NfL when added on top of clinical features, plasma p-tau$_{181}$, and APOE ε4 genotype (area under the curve [AUC] = 0.832 vs. AUC = 0.650 among CU, AUC = 0.853 vs. AUC = 0.805 among MCI) in predicting A+T+C+.

Discussion: AD-RAI outperformed plasma NfL in predicting syndromal conversion of early AD.

KEYWORDS
Alzheimer's disease, machine learning, magnetic resonance imaging, mild cognitive impairment, neurodegeneration, neurofilament light, phosphorylated tau, plasma biomarkers

Highlights

- AD-RAI outperformed plasma NfL in predicting syndromal conversion among early AD.
- AD-RAI showed better metrics than volumetric hippocampal measures in predicting syndromal conversion.
- Combining clinical features, plasma p-tau$_{181}$ and apolipoprotein E (APOE) with AD-RAI is the best model for predicting syndromal conversion.

1 | BACKGROUND

The risk of conversion to the next cognitive syndromal stage in subjects with early Alzheimer's disease (AD) varies with individuals. AD is currently defined biologically by the presence of cerebral amyloid β (Aβ) (A+) and tauopathy (T+).[1] Among subjects harboring Aβ and tauopathy who are cognitively unimpaired (CU) (i.e., preclinical AD) or have mild cognitive impairment (MCI) (i.e., prodromal AD), less than half of these subjects progress to the next syndromal stage within 5 years.[2,3] Therefore, subjects with a low risk of conversion may require only regular monitoring, whereas those with high risks may be prioritized for more aggressive interventions. Moreover, knowledge of the rate of cognitive decline may affect the design and interpretation of the results of clinical trials for early AD.[4] For example, a plausible reason explaining the statistically significant benefit of high-dose aducanumab observed only in EMERGE and not in ENGAGE could be related to the rapid cognitive decline observed in the placebo group of EMERGE.[5] Future trials should consider recruiting subjects with similar risks of syndromal conversion.

Although neurodegeneration (N+) is a non-specific biomarker for AD, studies have demonstrated that the presence of neurodegeneration in subjects with early AD predicts syndromal conversion. AD subjects with neurodegeneration have more than two times higher risk of syndromal conversion than those without it within 5 years.[2] Early pathological study also showed that markers of neurodegeneration (e.g., loss of synapse) more significantly correlate with cognitive performance than the quantity of Aβ plaques or tauopathy.[6] Hence, determining the severity of neurodegeneration is helpful in predicting the risk of syndromal conversion in early AD.

Technological advancements have allowed in vivo detection of Aβ, tauopathy, and neurodegeneration based on blood-based biomarkers. Conventional methods for the detection of Aβ and tauopathy include cerebrospinal fluid (CSF) assays and positron emission tomography (PET).[7] Neurodegeneration can be detected by PET, CSF, and magnetic resonance imaging (MRI). The cost and the relatively invasive nature of PET and CSF assay hindered their uses in daily practice. Recent studies have shown that plasma phosphorylated tau at threonine-181 (p-tau$_{181}$) alone reflects both cerebral Aβ burden and tauopathy.[8–10] For plasma neurofilament light chain (NfL), total tau (T-tau), and glial fibrillary acidic protein (GFAP) levels, which reflect different aspects of neurodegeneration, prior studies have shown that each of these neurodegeneration biomarkers' performance in predicting cognitive decline differ.[11–13] Plasma NfL was found to outperform plasma T-tau and performed similarly to GFAP in predicting cognitive decline.[14,15] Another study showed that combining plasma p-tau$_{181}$ with plasma NfL achieved the best performance in predicting syndromal conversion from MCI to dementia.[16]

Technological advancements have also been made in the development of MRI-based neurodegeneration biomarkers. Medial temporal lobe atrophy (MTA) or hippocampal atrophy is the most established MRI-based neurodegeneration biomarker for AD.[17,18] Recent studies showed that a machine-learning derived index, namely the AD-resemblance atrophy index (AD-RAI), outperformed hippocampal measures in detecting early AD and in predicting conversion among CU and MCI subjects.[19,20] AD-RAI was designed to reflect the similarity and severity of multi-brain region atrophy pattern characteristic of AD.[20–23] To date, AD-RAI is commercially available for use in clinical setting. Although MRI is less accessible than blood-based investigations, it offers the advantage of co-detecting other brain lesions (e.g., white matter hyperintensities), which may affect the risk of conversion and eligibility for receiving anti-amyloid therapies for prodromal AD.[24]

Since plasma NfL and AD-RAI likely capture different aspects of neurodegeneration,[14] their performances in predicting syndromal conversion among early AD likely differ. To date, there is no study comparing the relative performances and added values of incorporating plasma NfL and AD-RAI into clinical prediction models. In this study, we aimed to compare the performances of plasma NfL and AD-RAI on top of a simple clinical model plus plasma p-tau$_{181}$ and apolipoprotein E (APOE) ε4 in predicting syndromal conversion of early AD among CU and MCI subjects.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the available scientific literature on PubMed for articles examining neurodegeneration biomarkers in Alzheimer's disease (AD). Both plasma neurodegeneration biomarkers and MRI-based neurodegeneration biomarkers showed diagnostic and prognostic performance in early AD. However, no head-to-head studies comparing the diagnostic performance and prediction of disease progression between plasma neurofilament light chain (NfL) and machine learning-derived MRI-based biomarkers.
2. **Interpretation**: Our findings suggested that MRI-based Alzheimer's disease resemblance atrophy index (AD-RAI) outperformed plasma NfL and conventional volumetric hippocampal measures in predicting syndromal conversion of early AD by itself, or when combined with clinical features, plasma p-tau$_{181}$, and/or apolipoprotein E (APOE) ε4 genotype. The model incorporating clinical features, plasma p-tau$_{181}$, and APOE ε4 genotype with AD-RAI performed the best in predicting the syndromal conversion of early AD subjects.
3. **Future directions**: Further validation of the model in a large separate database is needed.

2 | METHODS

2.1 | Participants and cognitive assessment

All participants in this cohort study were enrolled from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. ADNI is a longitudinal multicenter study that provides clinical data, imaging, genetic, and biochemical biomarkers information for the early detection and

tracking of AD. More detailed information could be sought at http://adni.loni.usc.edu.[25]

In our study, the CU and MCI subjects from the ADNI Grand Opportunity/ADNI 2 study were included in the study if the ADNI database provides the following data: (1) baseline plasma p-tau$_{181}$ concentration, (2) baseline plasma NfL concentration, (3) baseline CSF A$\beta_{1\text{-}42}$ and CSF p-tau$_{181}$ levels, and (4) baseline structural MRI scans. Furthermore, to monitor the progression of the patients, all the patients underwent up to 4-year follow-up and the clinical assessments for determination of conversion were done annually. If the subjects were diagnosed as CU or MCI and diagnosis did not change at all available time points (0–48 months), we defined them as CU/MCI stable (C−). If the subjects were diagnosed as CU at baseline but converted to MCI or diagnosed as MCI at baseline but converted to dementia within 4 years, and without reversion reported at any available follow-up, we defined the subjects as CU-to-MCI converter or MCI-to-dementia converter (C+). Information on the change of subjects' diagnoses was downloaded from the ADNI website (DXSUM_PDXCONV_ADNIALL.csv and BLCHANGE.CSV).

Following the ADNI protocol, the CU subjects were diagnosed with a Mini-Mental State Examination (MMSE) score between 24 and 30 and a global Clinical Dementia Rating (CDR) of 0. And the MCI subjects were diagnosed with an MMSE score between 24 and 30 and a CDR of 0 or 0.5, with a memory box score of at least 0.5. The MCI subjects were also diagnosed with objective evidence of memory impairment, as determined by standardized memory tests, but with normal performance on other cognitive tests and preserved daily functioning. The dementia subjects were diagnosed with an MMSE score between 20 and 26 and a CDR of 1 or higher. The subjects with dementia had to meet the criteria of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association for probable AD.[26] A delayed recall of one paragraph from the Logical Memory II subscale of the Wechsler Memory Scale—Revised (maximum score of 25) was used for the memory criterion,[27] with cutoff scores based on education as follows: normal subjects ≥9 for 16 years of education, ≥5 for 8–15 years of education, and ≥3 for 0–7 years of education. The scores for subjects with MCI and subjects with AD were ≤8 for 16 years of education, ≤4 for 8–15 years of education, and ≤2 for 0–7 years of education.[28] Subjects having any significant neurological disease other than suspected incipient AD, such as Parkinson's disease, Huntington's disease, or known structural brain abnormalities including multiple lacunes or lacunes in a critical memory structure, infarction, or other focal lesions were excluded from our study. The Montreal Cognitive Assessment (MoCA) score was also collected to assess cognitive impairment severity.

2.2 | Fluid biomarkers sampling and processing

Blood sampling and processing were conducted by the ADNI protocol. Plasma p-tau$_{181}$ and plasma NfL concentration were analyzed by the Single Molecule Array (SiMoA) technique as the previous report.[9] In addition, the CSF A$\beta_{1\text{-}42}$, t-tau, and p-tau$_{181}$ were measured by Innogenetics/Fujirebio AlzBio3 immunoassay kits and the xMAP Luminex platform in the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center.[29] To assign a biological phenotype to each individual at baseline, previously defined thresholds were applied; less than 192 pg/mL for CSF A$\beta_{1\text{-}42}$ are defined as A+, and greater than 23 pg/mL for CSF p-tau$_{181}$ are defined as T+.[30]

2.3 | Neuroimaging

The 3D T1-weighted, T2-weighted, and FLAIR sequences were used for visual rating and neuroimaging analyses. The AD-RAI was generated by AccuBrain and calculated according to the atrophy degree of AD-related brain structures, including subcortical structures (e.g., hippocampus), ventricles, and cortical lobar regions. It was derived from an in-house training database, indicating the similarity in atrophy pattern between the subject's brain and those with AD dementia (ranging from 0 to 1). The details of the development of AD-RAI were described in our previous report.[19,20] Furthermore, we also compared AD-RAI with the traditional atrophy features including hippocampal volume (HV), and hippocampal fraction (HF, bilateral absolute HV over intracranial volume ratio), intracranial volume (ICV), which were all automatically generated by AccuBrain.

2.4 | Statistical analysis

Subjects were grouped based on three categories including baseline CSF A$\beta_{1\text{-}42}$ (A), CSF p-tau$_{181}$ concentration (T), and conversion within 4 years (C). For example, those subjects with CSF A$\beta_{1\text{-}42}$ positive (<192 pg/mL), CSF p-tau$_{181}$ positive (>23 pg/mL) and converted from CU to MCI or from MCI to AD within 4 years without any reversion reported were defined as A+T+C+, and others defined as not A+T+C+.

Categorical variables were described as numbers (proportion), and continuous variables as medians (interquartile range, IQR) or means ± standard deviation (SD). χ^2 tests or Fisher's exact tests were used for categorical variables and Student's *t*-tests or Mann–Whitney U tests for continuous variables. The effect size of image biomarkers and plasma biomarkers was estimated by calculating Cohen's *d*, and the cutoffs for the interpretation of Cohen's *d* are 0.2 (small), 0.5 (medium), and 0.8 (large).[23]

Univariate logistics regression was conducted to explore the association between outcomes and image biomarkers and blood-based biomarkers. The odds ratios (OR) and 95% confidence intervals (CIs) were obtained. Then we adjusted age, gender, education, and baseline MoCA score of each subjects with their image biomarkers, and plasma biomarkers, respectively, and used A+T+C+ or not as dependent variable to further explore the association between biomarkers and outcome.

We compared the prediction performances of the blood-based and MRI-based neurodegeneration biomarkers on top of clinical risk factors. First, we built a clinical model including age, gender, education, and MoCA score to evaluate the predicting ability of simple

characteristics and cognition assessment by multivariable logistic regression. AD-RAI or plasma NfL was then added on top of the clinical model to evaluate the performance metrics in predicting A+T+C+. Afterwards, we further combined the neurodegeneration biomarkers with the clinical model and plasma p-tau$_{181}$, and compared the prediction performances. The models were trained and validated with 10-fold cross-validation. The receiver operating characteristic (ROC) analysis and the area under the ROC curve (AUC) were employed to evaluate model identification performance. Based on Delong's method, $p < 0.05$ was considered statistically significant when comparing AUC values.[31] The sensitivity and specificity of the optimal cut-off point based on the Youden Index (J) of each model were reported to evaluate the diagnostic accuracy of different measures.[32] The reclassification was assessed using net reclassification index (NRI) and integrated discrimination index (IDI).[33] (Table S1) Since in our cohort the number of positive and negative cases was imbalanced, we used the arithmetic mean of sensitivity and specificity, to calculate the balanced accuracy instead of the standard accuracy.[34] We defined the best model as which included the fewest predictors and highest AUC. Furthermore, although APOE ε4 is the strongest genetic risk factor for AD, it has ethical issues when applying it in clinical practice. Irrespective of this issue, we also explored whether using the APOE ε4 genotype (ε4 carrier vs. non-carrier) improved the overall performance of the model. The analysis between groups and the performance of the models was trained and validated among CU and MCI groups separately.

In addition to the above analyses that categorized groups into A+T+C+ versus non-A+T+C, we also performed similar analyses with following groupings: (1) A+T+ versus non-A+T+ (Tables S2, S3, S4, S5, S6), (2) A+T+C+ versus A+T+C− (Table S7), and (3) A+C+ versus A+C− (Table S8).

All analyses were performed with SPSS version 26.0 and R software (version 4.1.3). Two-sided $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Participants

From June 2010 to December 2013, 589 subjects (mean [SD] age, 72.2 [6.9] years; 314 males [53.3%]) were enrolled in the ADNI database. 226 (38.4%) subjects were diagnosed as CU at baseline, which include 125 subjects with normal cognition and 91 subjects with subjective cognitive decline (SCD), while 363 (61.6%) subjects were diagnosed as MCI. The clinical demographic and characteristics are shown in Table 1, Table S9, and Figure S1.

3.2 | Biomarkers across diagnostic groups

The clinical demographic and characteristics of the A+T+C+ and non-A+T+C+ subjects are shown in Table 1. The CU subjects who were A+T+C+ were older ($p = 0.003$), with lower MoCA scores at baseline ($p = 0.050$) compared with those who were not A+T+C+. Among the CU group, only AD-RAI was significantly higher among A+T+C+ subjects with a large effect size ($p = 0.004$, Cohen's $d = 1.064$). The plasma NfL was marginally higher for the A+T+C+ subjects with a small effect size ($p = 0.019$, Cohen's $d = 0.314$). There were no differences in all other imaging biomarkers or plasma p-tau$_{181}$ concentration between the A+T+C+ and the non-A+T+C+ CU subjects, with corresponding small to medium effect sizes (Table 1 and Figure 1A). Those MCI subjects who were A+T+C+ had lower baseline MMSE ($p < 0.001$) and MoCA ($p < 0.001$) scores. Among MCI subjects, all the imaging biomarkers and both plasma p-tau$_{181}$ and plasma NfL were significantly different between A+T+C+ and not A+T+C+ subjects ($p < 0.001$). Among them, both AD-RAI (Cohen's $d = 0.960$) and plasma p-tau$_{181}$(Cohen's $d = 0.985$) showed large effect sizes of group difference (Table 1 and Figure 1B). Spearman's correlation showed no significant correlation between AD-RAI and plasma NfL among CU subjects (rho = −0.03, $p = 0.671$), and there was a weak but significant correlation between AD-RAI and plasma NfL among MCI subjects (rho = 0.20, $p = 0.0001$) (Figure S2).

3.3 | Association between neurodegeneration biomarkers and syndromal conversion

Multivariate logistic regression showed that higher AD-RAI was associated with A+T+C+ among CU subjects independent of age, gender, education, and baseline MoCA score (adjusted OR [aOR] 24.225; 95% CI, 2.785–210.754; $p = 0.004$, Table 2, model 1). Additional adjustment with respect to APOE ε4 genotype also yielded similar findings to that of model 1 above (Table 2, model 2).

Among MCI subjects, AD-RAI (aOR 10.016; 95% CI, 4.367–22.972), HV, HF, plasma p-tau$_{181}$, and plasma NfL all showed significant associations with A+T+C+ ($p < 0.001$, Table 3, model 1). Additional adjustment with respect to APOE ε4 genotype also yielded similar findings to that of model 1 above, except that the association between plasma NfL and A+T+C+ became insignificant ($p = 0.103$) (Table 3, model 2). Overall, multivariate logistic regression showed that among all independent variables, AD-RAI had the highest aOR in the association with A+T+C+ among CU or MCI subjects.

3.4 | Model selection and comparison for syndromal conversion

We next examined the accuracies of different biomarkers in predicting A+T+C+ on top of the clinical model (including age, gender, education, and baseline MoCA score). Adding plasma p-tau$_{181}$ on top of the clinical model improved the AUC from 0.615 to 0.659 and from 0.712 to 0.788, among CU and MCI, respectively. When we added AD-RAI on top of the clinical model, AUC improved from 0.615 to 0.768 and from 0.712 to 0.779 among CU and MCI subjects, respectively. The AUC was the lowest with adding plasma NfL on top of the clinical model when compared with adding plasma p-tau$_{181}$ or AD-RAI (Figure 2).

TABLE 1 Cohort characteristics.

Characteristics	CU ($n = 226$)			MCI ($n = 363$)		
	A+T+ and converted to MCI ($n = 11$)	Non-A+T+ or not converted to MCI ($n = 215$)	*p*-Value	A+T+ and converted to AD dementia ($n = 85$)	Non-A+T+ or not converted to AD dementia ($n = 278$)	*p*-Value
Age (years), mean (SD)	78.4 ± 5.9	72.4 ± 5.8	0.003	72.9 ± 6.7	71.5 ± 7.5	0.051
Male (n [%])	6(54.5)	102(47.4)	0.439	46(54.1)	160(57.6)	0.331
Education (years), mean (SD)	16.0 ± 2.0	16.8 ± 2.5	0.181	16.3 ± 2.6	16.2 ± 2.6	0.654
MMSE, mean (SD)	28.3 ± 1.8	29.1 ± 1.2	0.082	27.2 ± 1.8	28.3 ± 1.6	<0.001
MoCA, mean (SD)	24.1 ± 2.8	25.9 ± 2.4	0.050	21.5 ± 2.7	23.7 ± 2.9	<0.001
APOE ε4 genotype (n [%])	5(45.5)	61(28.4)	0.306	64(75.3)	109(39.2)	<0.001
AD-RAI, mean (SD)	0.5 ± 0.3	0.2 ± 0.2	0.004	0.7 ± 0.3	0.4 ± 0.3	<0.001
HV	6.2 ± 0.8	6.4 ± 0.7	0.593	5.5 ± 0.8	6.1 ± 0.9	<0.001
HF	0.4 ± 0.1	0.4 ± 0.1	0.083	0.4 ± 0.1	0.4 ± 0.1	<0.001
ICV	1516.9 ± 101.1	1480.6 ± 149.5	0.308	1510.9 ± 161.5	1502.1 ± 152.3	0.994
CSF $A\beta_{42}$ (pg/mL), mean (SD)	198.6 ± 142.5	211.4 ± 109.7	<0.001	132.3 ± 22.3	211.1 ± 178.5	<0.001
CSF p-tau_{181}(pg/mL), mean (SD)	45.3 ± 18.4	34.2 ± 17.8	0.024	63.9 ± 25.7	35.5 ± 20.7	<0.001
CSF t-tau(pg/mL), mean (SD)	74.9 ± 48.0	65.9 ± 36.3	0.542	128.4 ± 64.3	79.3 ± 58.3	<0.001
Plasma p-tau_{181}(pg/mL), mean (SD)	18.8 ± 9.1	14.8 ± 10.3	0.066	26.4 ± 15.2	16.0 ± 8.8	<0.001
Plasma NfL, (pg/mL), mean (SD)	41.9 ± 13.3	34.5 ± 23.5	0.019	46.2 ± 18.8	36.8 ± 19.5	<0.001

Note: Values are mean ± standard deviation or numbers (%).
Abbreviations: Aβ, amyloid β; AD-RAI, AD resemblance atrophy index; APOE, Apolipoprotein E; CSF, cerebrospinal fluid; HF, hippocampus fraction; HV, hippocampus volume; ICV, intracranial volume; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; SD, standard deviation.

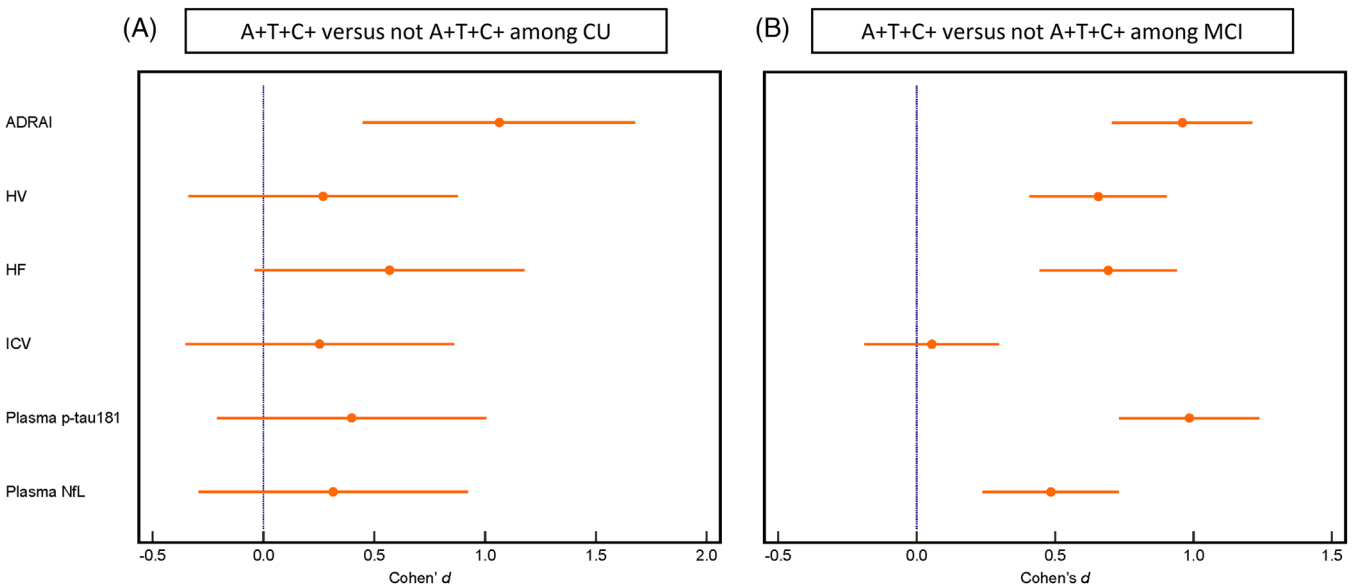

FIGURE 1 Effect sizes of image biomarkers and plasma biomarker levels change by ATC groups ([A] CU group, $n = 226$, A+T+C+ $n = 11$, [B] MCI subgroup, $n = 363$, A+T+C+ $n = 85$). The effect size of group differences was estimated by calculating Cohen's *d*, in which the dependent variable is the A+T+C+ or not and the independent variable was the log (transformed) biomarkers. The error bars represent the 95% CIs. AD-RAI, AD resemblance atrophy index; CU, cognitively unimpaired; HV, hippocampus volume; HF, hippocampus fraction; ICV, intracranial volume; MCI, mild cognitive impairment; NfL, neurofilament light chain.

TABLE 2 Univariate and multivariate logistic regression between biomarkers and A+T+C+ or not among CU subjects ($n = 226$).

	Univariate logistic regression		Multivariate logistic regression			
			Model 1[a]		Model 2[b]	
Variables	Crude OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-Value
Age	1.187 (1.062–1.327)	0.002	N/A	N/A	N/A	N/A
Gender	1.329 (0.394–4.488)	0.646	N/A	N/A	N/A	N/A
Education	0.290 (0.882–0.698)	0.290	N/A	N/A	N/A	N/A
MoCA	0.760 (0.595–0.972)	0.029	N/A	N/A	N/A	N/A
APOE ε4 genotype	2.104 (0.619–7.150)	0.233	3.786 (0.945–15.172)	0.060	N/A	N/A
AD-RAI	21.196 (3.013–149.096)	0.002	24.225 (2.785–210.754)	0.004	42.318 (3.865–463.285)	0.002
HV	0.666 (0.281–1.575)	0.355	0.691 (0.250–1.911)	0.447	0.623 (0.212–1.834)	0.390
HF	0.000 (0.000–2.090)	0.064	0.000 (0.000–18.512)	0.106	0.000 (0.000–3.900)	0.071
ICV	1.002 (0.998–1.006)	0.427	1.003 (0.997–1.009)	0.360	1.003 (0.997–1.010)	0.297
Plasma p-tau$_{181}$	1.027 (0.984–1.072)	0.218	1.031 (0.978–1.087)	0.257	1.027 (0.971–1.086)	0.347
Plasma NfL	1.008 (0.992–1.024)	0.332	0.999 (0.972–1.027)	0.939	1.002 (0.975–1.030)	0.873

Abbreviations: APOE, apolipoprotein E; AD-RAI, AD resemblance atrophy index; CI, confidence interval; HF, hippocampus fraction; HV, hippocampus volume; ICV, intracranial volume; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; OR, odds ratio.
[a]Adjusted for variables included age, gender, education, and baseline MoCA score.
[b]Adjusted for variables contained in model 1 plus APOE ε4 genotype.

TABLE 3 Univariate and multivariate logistic regression between biomarkers and A+T+C+ or not among MCI subjects ($n = 363$)

	Univariate logistic regression		Multivariate logistic regression			
			Model 1[a]		Model 2[b]	
Variables	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.025 (0.992–1.060)	0.143	N/A	N/A	N/A	N/A
Gender	0.870 (0.534–1.418)	0.870	N/A	N/A	N/A	N/A
Education	1.021 (0.930–1.121)	0.660	N/A	N/A	N/A	N/A
MoCA	0.759 (0.690–0.835)	<0.001	N/A	N/A	N/A	N/A
APOE ε4 genotype	4.725 (2.730–8.178)	<0.001	4.841 (2.665–8.791)	<0.001	N/A	N/A
AD-RAI	13.353 (6.264–28.464)	<0.001	10.016 (4.367–22.972)	<0.001	9.850 (4.141–23.430)	<0.001
HV	0.468 (0.345–0.633)	<0.001	0.527 (0.373–0.744)	<0.001	0.578 (0.402–0.830)	0.003
HF	0.000 (0.000–0.001)	<0.001	0.000 (0.000–0.002)	<0.001	0.000 (0.000–0.004)	<0.001
ICV	1.000 (0.999–1.002)	0.656	1.002 (1.000–1.004)	0.117	1.002 (1.000–1.005)	0.057
Plasma p-tau$_{181}$	1.096 (1.065–1.127)	<0.001	1.081 (1.050–1.112)	<0.001	1.064 (1.033–1.095)	<0.001
Plasma NfL	1.022 (1.010–1.034)	<0.001	1.019 (1.005–1.033)	0.007	1.011 (0.998–1.025)	0.103

Abbreviations: APOE, apolipoprotein E; AD-RAI, AD resemblance atrophy index; CI, confidence interval; HF, hippocampus fraction; HV, hippocampus volume; ICV, intracranial volume; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; OR, odds ratio.
[a]Adjusted for variables included age, gender, education, and baseline MoCA score.
[b]Adjusted for variables contained in model 1 plus APOE ε4 genotype.

We then added AD-RAI on top of the model combining clinical features and plasma p-tau$_{181}$, and attained AUCs of 0.786 and 0.828 among CU and MCI subjects, respectively. In contrast, when combining plasma NfL with the same model, the AUCs were 0.642 and 0.782 among CU and MCI subjects, respectively, which were significantly lower than that obtained with AD-RAI (Figure 2).

The model combining clinical features, plasma p-tau$_{181}$, and APOE ε4 genotype achieved AUC of 0.648 among CU, and 0.815 among MCI subjects. When we further added AD-RAI on top of the model combining clinical features, APOE ε4 genotype, and plasma p-tau$_{181}$, the AUC improved from 0.648 to 0.832 among CU, and from 0.815 to 0.853 among MCI subjects. When we combined plasma NfL with the

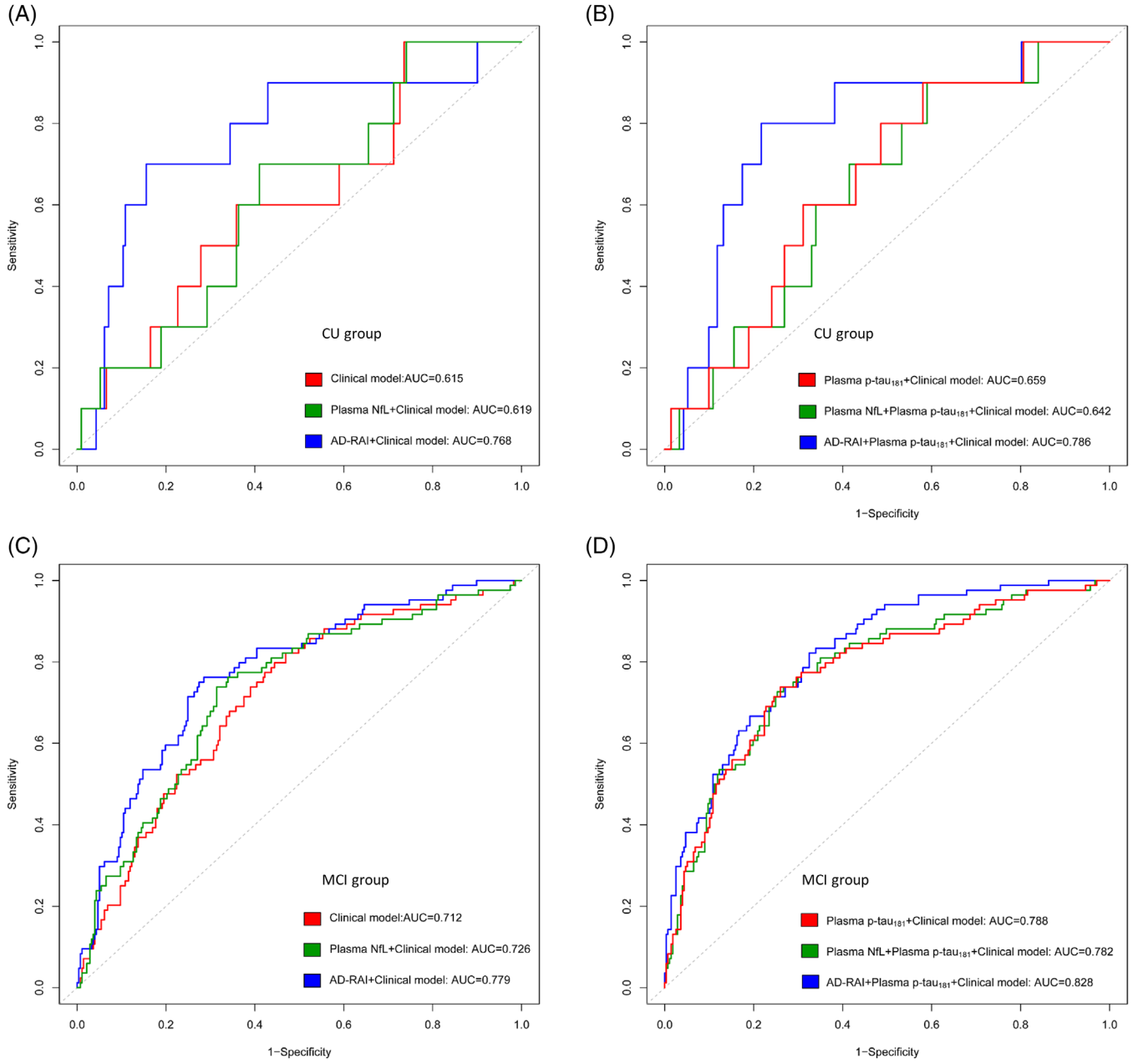

FIGURE 2 ROC for the model to predict A+T+C+. This figure shows the ROC curves of different models for predicting those subjects who are already harboring A+T+ and will progress to the next sydromal stage (i.e., CU-to-MCI converters and MCI-to-dementia converters) within 4 years. (A,B) The ROC curves among CU subjects ($n = 226$). (C,D) The ROC curves among MCI subjects. The clinical model included age, gender, education, and baseline MoCA score. AD-RAI, AD resemblance atrophy index; CU, cognitively unimpaired; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; ROC, receiver operating characteristic.

same model, the AUCs were only 0.650 and 0.805 among CU and MCI subjects, respectively (Table 4).

Note further that we also compared AD-RAI with other conventional MRI-based neurodegeneration biomarkers (i.e., HV, HF) in predicting A+T+C+. AD-RAI outperformed other conventional MRI-based biomarkers in predicting A+T+C+ (Table 4).

Overall among the various combinations, the best model in predicting A+T+C+ was combining clinical model with plasma p-tau$_{181}$, APOE ε4 genotype, and AD-RAI. The AUC (95% CI), sensitivity, specificity, balanced accuracy were 0.832 (0.719–0.945), 0.900, 0.666, 0.783, and 0.853 (0.808–0.898), 0.821, 0.794, and 0.808 for CU and MCI subjects, respectively (Table 4).

Further analyses using other groupings also yielded similar findings, that AD-RAI outperformed plasma NfL in predicting A+T+C+ from A+T+C− (Table S7) or A+C+ from A+C− (Table S8) among CU and MCI subjects, and the best model was one that combined clinical model with plasma p-tau$_{181}$, APOE ε4 genotype, and AD-RAI.

TABLE 4 Performance metrics of models for the prediction of A+T+C+.

	CU group ($n = 226$)					MCI group ($n = 363$)				
Variables	AUC (95% CI)	Sensitivity	Specificity	Balanced Accuracy	*p*-Value[b]	AUC (95% CI)	Sensitivity	Specificity	Balanced Accuracy	*p*-value[b]
Biomarkers on top of clinical model										
Clinical model[a]	0.615 (0.458–0.771)	0.900	0.566	0.733	0.012	0.712 (0.651–0.773)	0.762	0.625	0.694	0.006
+plasma NfL	0.619 (0.432–0.806)	0.700	0.410	0.555	0.012	0.726 (0.663–0.787)	0.738	0.684	0.711	0.016
+HV	0.613 (0.447–0.779)	0.400	0.840	0.620	0.010	0.748 (0.689–0.807)	0.750	0.701	0.726	0.018
+HF	0.668 (0.479–0.858)	0.600	0.576	0.588	0.019	0.755 (0.697–0.813)	0.714	0.701	0.708	0.045
+ICV	0.649 (0.475–0.822)	0.800	0.449	0.625	0.005	0.711 (0.649–0.772)	0.762	0.589	0.676	0.005
+AD-RAI	0.768 (0.500–0.938)	0.800	0.741	0.771	Ref.	0.779 (0.500–0.938)	0.738	0.744	0.741	Ref.
Biomarkers on top of clinical model and plasma p-tau$_{181}$										
Clinical model+ plasma p-tau$_{181}$	0.659 (0.521–0.796)	0.700	0.500	0.600	0.019	0.788 (0.731–0.845)	0.798	0.704	0.751	0.025
+plasma NfL	0.642 (0.474–0.810)	0.900	0.411	0.656	0.019	0.782 (0.732–0.846)	0.726	0.748	0.737	0.023
+AD-RAI	0.786 (0.637–0.935)	0.900	0.675	0.788	Ref.	0.828 (0.780–0.876)	0.905	0.594	0.750	Ref.
Biomarkers on top of clinical model, plasma p-tau$_{181}$, and APOE ε4 genotype										
Clinical model + APOE ε4 genotype	0.675 (0.481–0.869)	0.600	0.769	0.685	0.017	0.778 (0.720–0.835)	0.643	0.831	0.737	0.007
+plasma NfL	0.658 (0.492–0.825)	0.600	0.736	0.668	0.016	0.770 (0.713–0.827)	0.714	0.751	0.733	0.006
+AD-RAI	0.815 (0.678–0.951)	0.800	0.783	0.792	Ref.	0.825 (0.780–0.876)	0.905	0.594	0.750	Ref.
Clinical model + APOE ε4 genotype + plasma p-tau$_{181}$	0.648 (0.473–0.822)	0.600	0.797	0.699	0.013	0.815 (0.763–0.868)	0.762	0.701	0.732	0.008
+plasma NfL	0.650 (0.571–0.871)	0.500	0.759	0.630	0.011	0.805 (0.750–0.859)	0.738	0.791	0.765	0.005
+AD-RAI	0.832 (0.719–0.945)	0.900	0.666	0.783	Ref.	0.853 (0.808–0.898)	0.821	0.794	0.808	Ref.

Abbreviations: APOE, apolipoprotein E; AD-RAI, AD resemblance atrophy index; AUC, area under curve; CI, confidence interval; CU, cognitively unimpaired; HF, hippocampus fraction; HV, hippocampus volume; ICV, intracranial volume; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain.

[a]The clinical model included age, gender, education, and baseline MoCA score.

[b]The *p*-values of pairwise comparison by Delong's test were reported. The performance of neurodegeneration biomarkers were tested in models including: (1) on top of clinical model (including age, gender, education, baseline MoCA score), (2) on top of clinical model and plasma p-tau$_{181}$, (3) on top of clinical model and APOE ε4 genotype, and (4) on top of clinical model, plasma p-tau$_{181}$ and APOE ε4 genotype. All the pairwise comparison were using the models with AD-RAI as reference.

4 | DISCUSSION

In this study, we compared the performance of AD-RAI versus that of a blood-based neurodegeneration biomarker (i.e., plasma NfL) when incorporated into a model combining clinical model, plasma p-tau$_{181}$, and APOE ε4 genotype in predicting the 4-year cognitive decline risk of A+T+ CU or MCI subjects . The effect size of AD-RAI between A+T+C+ and non-A+T+C+ subjects was double of that of plasma NfL in differentiating between the groups. Moreover, logistic regression showed a greater association between AD-RAI and A+T+C+ than plasma NfL. We found that AD-RAI outperformed plasma NfL in predicting conversion to the next syndromal stage among early AD on top of clinical factors and plasma p-tau$_{181}$.

A plausible reason explaining the superiority of AD-RAI over plasma NfL included that AD-RAI reflects the severity of the loss of specific brain tissue (e.g., neuropil in the cortex) that have strong correlation with cognitive function.[23,35–37] In addition, AD-RAI reflects another dimension of neurodegeneration, which is the degree of similarity in the pattern of brain atrophy to that of AD subjects. In contrast, plasma NfL reflects mainly axonal loss,[38] which is less specific than AD-RAI since its level could not reflect the unique pattern of AD-related brain atrophy. Our results were consistent with that of another study showing that MRI-based HV, which reflects neuropil quantity, was the strongest predictor for cognitive decline when compared with plasma-based neurodegeneration biomarkers (e.g., NfL) among SCD subjects.[14] Note that the present study also showed that AD-RAI outperformed traditional volumetric hippocampal measures in predicting syndromal conversion. This finding was again similar to a previous study.[20]

We observed that not only was plasma NfL inferior to AD-RAI in predicting syndromal conversion, it also had no additional predictive value in predicting syndromal conversion when added to the model combining clinical features and plasma p-tau$_{181}$. This result contradicted a previous study showing that plasma NfL had additional value in predicting SCD-to-MCI or dementia conversion.[14] This discrepancy may also be explained by differences in the pathology profiles of the subjects. The previous study did not define the AD pathological profile of the subjects (i.e., A+T+), whereas in the present study we considered A+T+ status as defined by CSF biomarkers for the outcomes. Plasma NfL was reported to be an AD-nonspecific biomarker for neuronal injury independent of Aβ pathology.[39,40] In the previous study, 20% of converters were diagnosed as non-AD dementia. In contrast, we only included AD dementia and excluded subjects with neurological conditions other than AD incipient. The concentration of plasma NfL is also elevated in frontotemporal dementia,[41] Parkinson's disease,[42] cerebral small vessel disease.[43] The underlying disease pathology may thus influence the association between plasma NfL and cognitive decline.

We observed that 30.1% of CU subjects and 54.8% of MCI subjects were harboring A+T+ and only 15.9% of preclinical AD and 41.1% prodromal AD showed syndromal conversion within 4 years. The proportion of A+T+ among CU was higher in our study than previous studies where the reported prevalence was around 7.2%—12.5%, among which roughly 30%–80% progressed in 5–10 years.[44] This discrepancy may be caused by difference in methods for detecting A+T+. Previous study used PET to evaluate the amyloid and tau burden, whereas we used CSF biomarkers in the present study. It has been reported that changes in amyloid load and tauopathy measured by PET exceeded the respective thresholds later than CSF biomarkers over AD disease course, and was associated with faster progression of clinical symptoms.[45] This probably explains why previous study reported a lower prevalence but a greater conversion rate among CU subjects than us. On the other hand, the proportion and progression of A+T+ among MCI subjects are in line with previous reports, which showed a prevalence varying from 28% to 60% among MCI subjects with about 40%–50% progressed to AD dementia within a relatively short follow-up period.[4,46,47] These findings highlighted the need to not only use biomarkers for Aβ and tauopathy to define AD, but also consider utilizing neurodegeneration biomarkers to predict the speed of cognitive decline. Knowing the risk of syndromal conversion among preclinical or prodromal AD will likely affect the management strategies and treatment responses to interventional drugs in clinical trials.

Adding AD-RAI on top of clinical features and plasma p-tau$_{181}$ achieved a high sensitivity of around 90% among both CU and MCI subjects. Such a high sensitivity will ensure detection of the majority of A+T+C+ subjects. However, the specificity was around 60%. Hence, in situations where confirming A+T+ status is essential (e.g., administration of anti-amyloid therapy, recruitment into AD-specific preventive clinical trials), further tests (e.g., PET, CSF assays) need to be arranged to confirm Aβ and tau status.

The present study also showed that combining APOE ε4 genotype would increase the model performance in predicting syndromal conversion. Several studies have shown similar results that by combining APOE ε4 with plasma p-tau$_{181}$ or cortical atrophy, predictive value of conversion increased further.[48,49] Besides the link between APOE ε4 and amyloid-β peptide aggregation and clearance, APOE ε4 may also relate to blood-brain barrier damage, influence glial reactions, promote tau-induced neurodegeneration and atrophy, which all may lead to cognitive impairment.[50] Furthermore, we found that APOE ε4 achieved the best performance in differentiating A+T+ among both CU and MCI. It is also noteworthy that among CU subjects, both plasma p-tau$_{181}$ and AD-RAI did not yield any improvement in the prediction model when combined with APOE ε4. APOE ε4 genotype is a strong indicator of Aβ burden, which is usually considered to be the first pathological change in the disease cascade.[51,52] APOE ε4 allele carriers have a high rate of conversion to PiB-positive that happens years before the onset of clinical symptoms.[53] APOE ε4 genotype is, therefore, more sensitive to the early pathological change than tau or neurodegeneration biomarkers in the asymptomatic phase. Hence, for classification of A+T+ among CU subjects, model including only clinical features and APOE ε4 genotype already performed very well. However, genetic testing poses certain ethical, social, actuarial, and legal problems.[54] The clinical application of APOE εε4 should be taken with caution regarding the difficulties of disclosing testing results to the subjects and their relatives.

AD-RAI requires only 3D T1/FLAIR MRI sequences and the software takes about 10 min to generate the results back to the end user after the images are being uploaded to the cloud platform. Nonetheless, it still requires an MRI scanner, which is less widely applicable (e.g., contraindications of MRI include subjects with metallic implants and claustrophobia) and probably more costly when compared with blood-based biomarkers. Note however that on the other hand, MRI can provide other useful information (e.g., presence of cerebrovascular lesions) that may affect the prognosis and management but cannot be captured by current blood-based technologies. Overall, our study provides important data on the additional value of adding MRI or AD-RAI so that clinicians or researchers can decide whether AD-RAI should be used or not based on the purpose and resources available in a particular circumstance.

Our study has several limitations. First, although we used 10-fold validation to reduce the test error rate of our model, further validation of our model is needed in a separate cohort. Second, our sample was of moderate size, especially among CU subjects. More CU subjects will need to be recruited in future study. Third, since plasma Aβ42/Aβ40 was not available in the ADNI database, we were unable to explore its prediction value. Note however that previous study showed that removing plasma Aβ42/Aβ40 from a model including plasma p-tau$_{181}$ and brief cognitive tests did not affect the performance in predicting AD syndromal conversion.[48] Fourth, apart from measures of AD neurodegeneration, there are other potential factors, in particular vascular factors (e.g., presence of cerebral small vessel disease, blood pressure) that may also affect the rate of cognitive decline.[55] Fifth, biofluid biomarkers measurements may differ with different processing methods. Further exploration will need to determine whether such variations may affect the predictive performance of plasma NfL. Last, apart from plasma NfL, we did not compare AD-RAI with other neurodegeneration biomarkers, such as plasma t-tau or GFAP, plasma brain-derived tau,[56] electroencephalography (EEG), or magnetoencephalography (MEG). Note however that previous studies have already shown the superiority of plasma NfL over plasma t-tau in predicting cognitive decline.[13] While EEG/MEG can detect the change of brain wave patterns that are indicative of AD, their uses as non-invasive means to obtain neurodegeneration biomarkers for diagnosis and prognostication warrant further explorations.[57,58]

4.1 | Conclusion

AD-RAI outperformed plasma NfL in predicting syndromal conversion among preclinical and prodromal AD subjects. Combination of clinical features, plasma p-tau$_{181}$, APOE ε4 genotype, and AD-RAI provides the best model in identifying early AD subjects with high risk of conversion to next syndromal stage. The validity of this model needs to be confirmed in a separate larger cohort.

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CONFLICT OF INTEREST STATEMENT

Lin Shi is the director of BrainNow Medical Technology Limited. Vincent Chung Tong Mok is the chief medical consultant of BrainNow Medical Technology Limited. Lei Zhao and Yishan Luo are employed by BrainNow Medical Technology Limited. All other authors report no financial relationships with commercial interests. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided written informed consent approved by the institutional review board of each ADNI participating institution.

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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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