Diagnostic Performance of MRI-based Alzheimer's Disease Resemblance Atrophy Index and Plasma-Based Biomarkers on Alzheimer's Disease

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Background and Objective

Although positron emission tomography (PET) or cerebrospinal fluid measurements of amyloid and tau burden are available for the detection of Alzheimer's disease pathology, such methods are invasive and not easily accessible. Recent studies show that Alzheimer's Disease-resemblance atrophy index (AD-RAI), an MRI-based machine learning-derived biomarker, and plasma-based biomarkers can be used as accurate biomarkers for Alzheimer's disease pathology. We aim to evaluate the diagnostic metrics of AD-RAI and plasma-based biomarkers for detecting Alzheimer's disease.

Methods

We recruited 69 subjects from the CU-SEEDS (The **C**hinese **U**niversity of Hong Kong-**S**creening for **E**arly AlzhEimer's **D**iseaSe) study who were stroke-free and had different degrees of cognitive impairment: 8 cognitive unimpaired [CU], 26 with subjective cognitive decline [SCD], 21 with mild cognitive impairment [MCI] and 14 with dementia. All subjects underwent ^{11}C- PIB and ^{18}F-T807 PET to measure pathological Aβ deposition (A+) and tau burden (T+). Subjects received structural MRI for deriving AD-RAI. Plasma levels of Aβ40, Aβ42, total tau (t-tau), phosphorylated tau at 181 (p-tau181), and neurofilament light chain (NfL) were measured by Single Molecule Array (SiMoA) assays.

Results

Among 69 subjects (mean [SD] age, 67.7 [6.8] years; 28 men [40.6%]), 25 (36.23%) subjects were confirmed to be A+ and T+. AD-RAI, plasma p-tau 181, and plasma Aβ42 were associated with A+T+ after adjusting for age, gender, and education (p<0.01). AD-RAI individually outperformed all plasma-based biomarkers (AUC=0.911; Sensitivity=0.826; Specificity=0.905). The combination of AD-RAI, p-tau181 and Aβ42 yielded the best diagnostic metrics for detecting A+T+ subjects (AUC=0.957; Sensitivity=0.870; Specificity=0.929).

Conclusion

A panel of AD-RAI, plasma p-tau, and plasma Aβ42 might help with screening and diagnosis of Alzheimer's disease.

Table 1. Summary of Demographics and Imaging

Characteristics	Total (n=69)	A+T+ (n=25)	Non-A+T+ (n=44)	P value
Age (years), mean (SD)	67.74±6.75	69.08±7.22	66.98±6.44	0.15
Male (n [%])	28(40.58)	7(28.00)	21(47.73)	0.11
Education (years), mean (SD)	9.36±4.40	9.04±4.70	9.55±4.26	0.66
HK-MoCA, mean (SD)	21.97±6.21	17.36±6.22	24.59±4.46	< 0.001*
HKLLT *z*-score in Trial 4, mean (SD)	-0.79±1.30	-1.89±0.72	-0.17±1.13	< 0.001*
AD-RAI, mean (SD)	0.37±0.39	0.71±0.38	0.19±0.25	< 0.001*
Subgroup diagnosis, n (%)				
HC	8	0	8	
SCD	26	3	23	
MCI	21	9	12	
Dementia	14	13	1	
Blood biomarkers, pg/ml, mean (SD)				
Aβ40	183.44±36.61	188.52±40.63	180.56±34.28	0.432
Aβ42	9.98±3.19	8.54±2.55	10.80±3.25	0.003
NfL	17.85±8.87	20.25±8.30	16.49±8.99	0.067
t-tau	2.23±1.27	2.65±1.69	2.00±0.90	0.029
p-tau 181	2.80±1.48	3.83±1.42	2.22±1.17	< 0.001*
Aβ42/ Aβ40	0.05±0.01	0.05±0.01	0.06±0.01	< 0.001*
p-tau 181/ Aβ42	0.35±0.35	0.55±0.48	0.24±0.18	< 0.001*

A+T+: Subjects harbouring beta-amyloid and tau; SD: Standard deviation; HK-MoCA: Hong Kong Version of the Montreal Cognitive Assessment; HKLLT: Hong Kong List Learning Test; AD-RAI: AD resemblance atrophy index; HC: Healthy control; SCD: Subjective cognitive decline; MCI: Mild cognitive impairment; Aβ40: beta-amyloid 40; Aβ42: beta-amyloid 42; NfL: Neurofilament Light Chain; t-tau: Total Tau; p-tau 181: Phosphorylated tau 181. The p-values represent the group difference between A+T+ and Non-A+T+ groups derived from the independent samples Mann-Whitney U test for continuous variables and the Chi-square test for binary variables. *represents a significant difference at p<0.05

Table 2. Univariate and Multivariate Logistic Regression of Plasma-based Biomarkers and ADRAI

	Univariate logistic regression				Adjusted for age gender education				Adjusted for age gender education +MoCA			
	95% C.I. for EXP(B)				95% C.I. for EXP(B)				95% C.I. for EXP(B)			
	Exp(B)	Lower	Upper	Sig.	Exp(B)	Lower	Upper	Sig.	Exp(B)	Lower	Upper	Sig.
p-tau 181	2.506	1.532	4.101	0.000	2.485	1.504	4.107	0.000	1.755	0.993	3.102	0.053
Aβ42	0.771	0.637	0.935	0.008	0.750	0.612	0.920	0.006	0.681	0.523	0.887	0.004
Aβ40	1.006	0.992	1.020	0.385	1.001	0.987	1.016	0.859	0.997	0.978	1.016	0.742
t-tau	1.588	0.970	2.602	0.066	1.581	0.951	2.630	0.078	1.269	0.772	2.085	0.348
NfL	1.050	0.990	1.113	0.105	1.037	0.974	1.104	0.253	1.007	0.933	1.086	0.867
Aβ42/ Aβ40	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.003	0.000	0.000	0.000	0.003
p-tau 181/ Aβ42	318.370	11.278	8987.020	0.001	269.933	8.809	8271.305	0.001	42.872	1.750	1050.164	0.021
ADRAI	55.016	9.354	323.567	0.001	313.527	21.439	4585.030	0.000	118.396	6.259	2239.721	0.001

Exp(B): Odds ratio; 95%C.I.: 95% Confidence interval; p-tau 181: Phosphorylated tau 181; Aβ42: beta-amyloid 42; Aβ40: beta-amyloid 40; t-tau: Total Tau; NfL: Neurofilament Light Chain; AD-RAI: AD resemblance atrophy index.

Table 3. Diagnostic Performance of Different Predictors

Predictors	AUC	Sensitivity	Specificity
Aβ42	0.893(0.795 to 0.954)	0.720	0.909
p-tau 181	0.863(0.759 to 0.934)	0.720	0.932
ADRAI	0.911(0.814 to 0.967)	0.826	0.905
p-tau 181+ Aβ42	0.912(0.819 to 0.967)	1	0.659
ADRAI+ p-tau 181+ Aβ42	0.957(0.875 to 0.992)	0.870	0.929
ADRAI+ p-tau 181	0.939(0.850 to 0.983)	0.870	0.881

AD-RAI: AD resemblance atrophy index; Aβ42: beta-amyloid 42; p-tau 181: Phosphorylated tau 181; AUC: Area under curve.