Magnetic resonance imaging–based machine learning to detect mild cognitive impairment associated with Alzheimer's disease: abridged secondary publication

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KEY MESSAGES

1. The Alzheimer's Disease Resemblance Atrophy Index (AD-RAI) is effective for identifying amyloid-positive and tau-positive pathology in patients with mild cognitive impairment.
2. The AD-RAI outperforms other conventional magnetic resonance imaging features (eg, hippocampus volume, hippocampus fraction, and medial temporal lobe atrophy score) in terms of accuracy, sensitivity, and specificity.
3. The AD-RAI can serve as a screening tool for the early detection and management of Alzheimer's disease.

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Introduction

Alzheimer's disease (AD) is the most common form of dementia. In Hong Kong, the prevalence of dementia is projected to triple in two decades, reaching 300 000 cases. Early diagnosis and treatment are crucial. Staging of AD is based on amyloid-beta plaques and tauopathy, facilitating early identification of preclinical and prodromal AD through biomarkers.[1] Individuals with mild cognitive impairment (MCI) who exhibit amyloid-positive and tau-positive (A+T+) pathology (ie, prodromal AD) have a substantially greater risk of experiencing short-term clinical progression.[2] The approval of lecanemab and donanemab for early AD treatment underscores the need for precise diagnosis. Standard detection involves cerebrospinal fluid assays and positron emission tomography, which are invasive and costly. Thus, the use of a non-invasive diagnostic method is pivotal for the early diagnosis of AD.

Structural magnetic resonance imaging (MRI) has been used to evaluate cognitive impairments and neurodegeneration through atrophy, which are key AD biomarkers.[3] Using advanced machine learning techniques and automated quantification tools for multiple brain regions, we developed an algorithm that produces the Alzheimer's Disease Resemblance Atrophy Index (AD-RAI), which captures the distinct pattern of atrophy across various brain regions associated with AD.[4] The AD-RAI outperformed hippocampal measures in predicting conversion among cognitively unimpaired individuals and patients with MCI.[4]

This study aimed to investigate the performance of AD-RAI for detecting A+T+ pathology in patients with MCI. The diagnostic performance of AD-RAI was compared with that of conventional AD imaging techniques: hippocampus volume and visual ratings of medial temporal lobe atrophy (MTA).

Methods

Chinese patients with MCI aged 50 to 80 years, whose primary language was Cantonese, were recruited from the community and the Prince of Wales Hospital, Hong Kong. Patients were excluded if they had a diagnosis of non-AD dementia, a history of stroke, parkinsonism, major psychiatric disease, or any significant neurological disease (eg brain tumour), or any contraindication for brain imaging. All patients were examined by an experienced dementia specialist to determine eligibility. Based on brain imaging results, patients were categorised as A+T+ (prodromal AD) or non–A+T+.

MCI was defined using the 2018 National Institute on Aging and Alzheimer's Association research framework. Memory complaints were assessed using the Chinese Abbreviated Memory Inventory; those who responded 'Yes' to any of its five questions were considered to have subjective memory complaints. Participants with an age-adjusted z-score of ≤-1 standard deviation in the Hong Kong List Learning Test trial 4, a score ≤16th percentile in the Hong Kong version of the Montreal Cognitive Assessment (MoCA), or a Clinical Dementia Rating of ≤0.5 were considered to have

MCI, regardless of independence in daily activities.

Structural MRI was conducted using 3.0 Tesla Achieva TX scanners (Philips Medical Systems, Best, Netherlands), focusing on the three-dimensional T1-weighted sequence. The AD-RAI was generated by assessing the extent of atrophy in AD-specific brain regions including the hippocampus, ventricles, and various cortical lobes. Diagnostic performance of the AD-RAI was compared with that of conventional atrophy metrics. MTA was rated on coronal images using the Scheltens 5-point scale; a score of ≥2 was defined as MTA.

Univariate logistic regression was conducted to assess the relationships between outcomes and various biomarkers. Adjustments were made for age, sex, education level, and baseline MoCA scores in relation to imaging features. A+T+ status was the dependent variable. Receiver operating characteristic curve analysis was used to assess the model's discriminative performance (sensitivity, specificity, and accuracy). Optimal cut-offs were determined using Youden's index: hippocampus volume of 6.07 mL, hippocampus fraction of 0.41%,[5] and AD-RAI of 0.4.

Results

In total, 26 male and 41 female patients (mean age, 68.8 years) were included in the analysis. Patients with and without A+T+ pathology were comparable in terms of baseline characteristics. However, patients with A+T+ pathology had higher AD-RAI (P<0.001), lower hippocampus volume (P<0.001), lower hippocampus fraction (P<0.001), and greater likelihood of displaying an MTA score ≥2 (P<0.001) [Table 1].

In the multivariable logistic regression, patients with A+T+ pathology were associated with higher AD-RAI (adjusted odds ratio [aOR]=101.29, P<0.001), lower hippocampus volume (aOR=11.38, P=0.001), lower hippocampus fraction (aOR=13.32, P=0.001), and greater likelihood of displaying an MTA score ≥2 (aOR=10.37, P<0.001), independent of age, sex, education level, and baseline MoCA score (Table 2).

The AD-RAI cut-off value of ≥0.4 achieved an area under the curve of 83.6%, which was higher than that for hippocampus volume of ≤6.07 mL (70.1%), hippocampus fraction of ≤0.41% (69.9%), and MTA score of ≥2 (71.6%). The AD-RAI cut-off of ≥0.4 had 81.8% sensitivity, 85.3% specificity, and 83.6% accuracy (Table 3).

Combining the clinical model with the AD-RAI cut-off of ≥0.4 achieved the highest area under the curve of 90.0%, with 84.9% sensitivity, 85.3% specificity, and 85.1% accuracy (Table 3). Combining the clinical model with other MRI features also led to improvements in performance metrics.

Discussion

The AD-RAI surpassed conventional brain atrophy metrics in identifying A+T+ pathology. This finding is consistent with our previous research, which indicates the superior efficacy of AD-RAI over hippocampus volume and hippocampus fraction in identifying A+T+ pathology among cognitively unimpaired individuals or patients with MCI. Typically, MTA and reductions in hippocampus volume are among the earliest changes detectable on structural MRI, manifesting years prior to the onset of clinical symptoms, and possibly indicative of progression from MCI to AD. However, multiple neuropathological subtypes of AD have been identified. Early-stage structural abnormalities observed on MTA might be minimal to mild, which

TABLE 1. Clinical characteristics of patients with Alzheimer's disease.

Characteristic	Total (n=67)	With amyloid-positive and tau-positive pathology (n=33)	Without amyloid-positive and tau-positive pathology (n=34)	P value
Age, y	68.8±5.1	66.6±7.1	67.8±6.2	0.306
Male sex	26 (38.8)	13 (39.4)	13 (38.2)	0.922
Education level, y	8.2±4.8	8.8±4.8	8.5±4.8	0.905
Hong Kong version of Montreal Cognitive Assessment	20.12±4.67	18.97±4.38	19.55±4.53	0.174
Alzheimer's Disease Resemblance Atrophy Index	0.19±0.24	0.72±0.33	0.45±0.39	<0.001
Hippocampus volume, mL	6.48±0.74	5.58±1.04	6.04±1.00	<0.001
Hippocampus fraction, %	0.46±0.05	0.4±0.06	0.43±0.06	<0.001
Intracranial volume, mL	1403.51±116.85	1377.36±119.88	1390.63±118.19	0.286
Medial temporary lobe atrophy score ≥2	32 (47.8)	23 (69.7)	9 (26.5)	<0.001

* Data are presented as mean±standard deviation or No. (%) of participants.

TABLE 2. Associations between biomarkers and amyloid-positive and tau-positive pathology in patients with Alzheimer's disease.

Variable	Univariate logistic regression		Multivariable logistic regression	
	Crude odds ratio (95% confidence interval)	P value	Adjusted odds ratio (95% confidence interval)	P value
Age, y	0.94 (0.87-1.02)	0.152	-	-
Sex	0.95 (0.36-2.55)	0.922	-	-
Education level, y	1.03 (0.93-1.14)	0.596	-	-
Hong Kong version of Montreal Cognitive Assessment	0.94 (0.85-1.05)	0.300	-	-
Alzheimer's Disease Resemblance Atrophy Index ≥0.4	26.10 (7.13-95.52)	<0.001	101.29 (10.81-948.79)	<0.001
Hippocampus volume ≤6.07, mL	5.52 (1.94-15.72)	0.001	11.38 (2.79-46.45)	0.001
Hippocampus fraction ≤0.41, %	7.97 (2.29-27.72)	0.002	13.32 (3.05-58.12)	0.001
Intracranial volume, mL	1.00 (0.99-1.00)	0.365	1.00 (0.99-1.00)	0.213
Medial temporal lobe atrophy score ≥2	6.39 (2.21-18.51)	0.003	10.37 (2.86-37.57)	<0.001

TABLE 3. Performance metrics of prediction models for amyloid-positive and tau-positive pathology in patients with Alzheimer's disease.

Variable	Area under the curve (95% confidence interval)	Sensitivity, %	Specificity, %	Accuracy, %
Alzheimer's Disease Resemblance Atrophy Index ≥0.4	83.6 (74.6-92.6)	81.8	85.3	83.6
Hippocampus volume ≤6.07, mL	70.1 (59.0-81.3)	69.7	70.6	70.2
Hippocampus fraction ≤0.41, %	69.9 (59.6-80.1)	51.5	88.2	70.2
Medial temporal lobe atrophy score ≥2	71.6 (60.7-82.6)	69.7	73.5	71.6
Clinical model	61.8 (48.0-75.6)	42.4	88.2	65.7
Clinical model + magnetic resonance imaging features				
+ Alzheimer's Disease Resemblance Atrophy Index ≥0.4	90.0 (82.6-97.4)	84.9	85.3	85.1
+ Hippocampus volume ≤6.07, mL	78.7 (67.0-90.5)	87.9	76.5	82.1
+ Hippocampus fraction ≤0.41, %	78.9 (67.6-90.1)	57.6	97.1	77.6
+ Medial temporal lobe atrophy score ≥2	80.0 (69.0-90.9)	72.7	82.4	77.6

is insufficient to predict underlying AD pathology. Our findings suggest that AD-RAI is more effective in detecting A+T+ pathology than localised atrophy measurements.

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Disclosure

The results of this research have been previously published in:

1. Cai Y, Fan X, Zhao L, et al. Comparing machine learning-derived MRI-based and blood-based neurodegeneration biomarkers in predicting syndromal conversion in early AD. Alzheimers Dement 2023;19:4987-98.

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