

Predicting Hippocampal Atrophy With PET And CSF Biomarkers In Alzheimer’S Disease: A Cross-sectional Study

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Background

Alzheimer’s disease is characterized by multiple pathological processes involving amyloid- β ($A\beta$) and tau. It remains uncertain which marker most reliably reflects the degree of hippocampal atrophy. We aimed to identify which biomarker best predicts hippocampal atrophy.

Methods

We conducted a retrospective cross-sectional study using Alzheimer’s Disease Neuroimaging Initiative data from 576 participants who underwent MRI, amyloid PET/CT, and CSF testing. Two independent neuroradiologists rated medial temporal atrophy (MTA) in each hippocampus using the Scheltens MTA scale. $A\beta$ Centiloids, meta-temporal tau-PET SUVR, CSF total tau (t-tau), phosphorylated tau (p-tau), $A\beta$ 42, and $A\beta$ 40 were the biomarkers evaluated. Multivariable logistic regression models adjusted for age, sex, and APOE ϵ 4 carrier status were used to assess associations with hippocampal atrophy, with $MTA \geq 2$ as the primary outcome. Discrimination was assessed using ROC curves and AUC, based on covariate-adjusted models.

Results

Participants with $MTA \geq 2$ were older (74.5 ± 6.9 years) and had worse cognitive status, with higher prevalence of mild cognitive impairment (MCI) (99; 40.4%) and Alzheimer’s disease dementia (61; 24.9%). They also showed higher amyloid burden ($A\beta$ Centiloids: 45.3 ± 50.3) and higher tau-PET uptake (meta-temporal tau-PET SUVR: 1.4 ± 0.3), along with lower CSF $A\beta$ 40 (16599.1 ± 5180.5) and $A\beta$ 42 (939.7 ± 510.3) (Table 1). Meta-temporal tau-PET SUVR (AUC 0.784, 95% CI 0.745-0.823, $n=523$) showed the best discrimination for $MTA \geq 2$ among all biomarkers evaluated. $A\beta$ 42 (AUC 0.759, 95% CI 0.709-0.809, $n=360$) demonstrated the highest discrimination among CSF biomarkers (Figure 1). Meta-temporal tau-PET SUVR (OR per 1 SD increase = 1.919, 95% CI 1.519-2.425, $p < 0.0001$) showed the strongest association with hippocampal atrophy in covariate-adjusted logistic regression, while $A\beta$ 42 (OR per 1 SD increase = 0.495, 95% CI 0.361-0.677, $p < 0.0001$) showed the strongest association among CSF biomarkers (Figure 2).

Table 1 | Demographics and clinical characteristics

	MTA < 2 (n = 331)	MTA $\geq$ 2 (n = 245)	P-value
Age, mean (SD), years	68.6 (6.9)	74.5 (6.9)	<0.0001*
Education, mean (SD), years	16.5 (2.3)	16.4 (2.4)	0.5414
Sex			0.0001*
Female	203 (61.3)	110 (44.9)	
Male	128 (38.7)	135 (55.1%)	
APOE ϵ 4 status			0.0706
Non-carrier	207 (62.5)	134 (54.7)	
Carrier	124 (37.5)	111 (45.3)	
Diagnosis			<0.0001*
CN	232 (70.1)	85 (34.7)	
MCI	94 (28.4)	99 (40.4)	
AD	5 (1.5)	61 (24.9)	
$A\beta$ Centiloids, mean (SD)	22.0 (35.1)	45.3 (50.3)	<0.0001*
Tau-PET, mean (SD)	1.2 (0.2)	1.4 (0.3)	<0.0001*
$A\beta$ 42, mean (SD)	1343.7 (716.8)	939.7 (510.3)	<0.0001*
$A\beta$ 40, mean (SD)	18900.0 (5731.3)	16599.1 (5180.5)	0.0001*
t-tau, mean (SD)	243.7 (99.2)	267.6 (127.0)	0.0467*
p-tau, mean (SD)	22.4 (11.0)	25.5 (15.0)	0.0254*

Continuous variables are presented as mean (SD), and categorical variables are presented as n (%). Group comparisons between $MTA < 2$ and $MTA \geq 2$ were performed using independent-samples t-tests for continuous variables (age, education, $A\beta$ centiloids, Tau-PET, $A\beta$ 42, $A\beta$ 40, t-tau, and p-tau) and Pearson’s chi-square test for categorical variables (sex, APOE ϵ 4 status, and diagnosis). Analyses were restricted to participants with known APOE ϵ 4 status. Abbreviations: AD, Alzheimer’s disease dementia; APOE ϵ 4 (APOE4), apolipoprotein E ϵ 4 allele; $A\beta$, amyloid- β ; CN, cognitively normal; MCI, mild cognitive impairment; MTA, medial temporal atrophy (Scheltens scale); $MTA \geq 2$, medial temporal atrophy cutoff ≥ 2 ; SD, standard deviation; SUVR, standardized uptake value ratio. * $P < 0.05$.

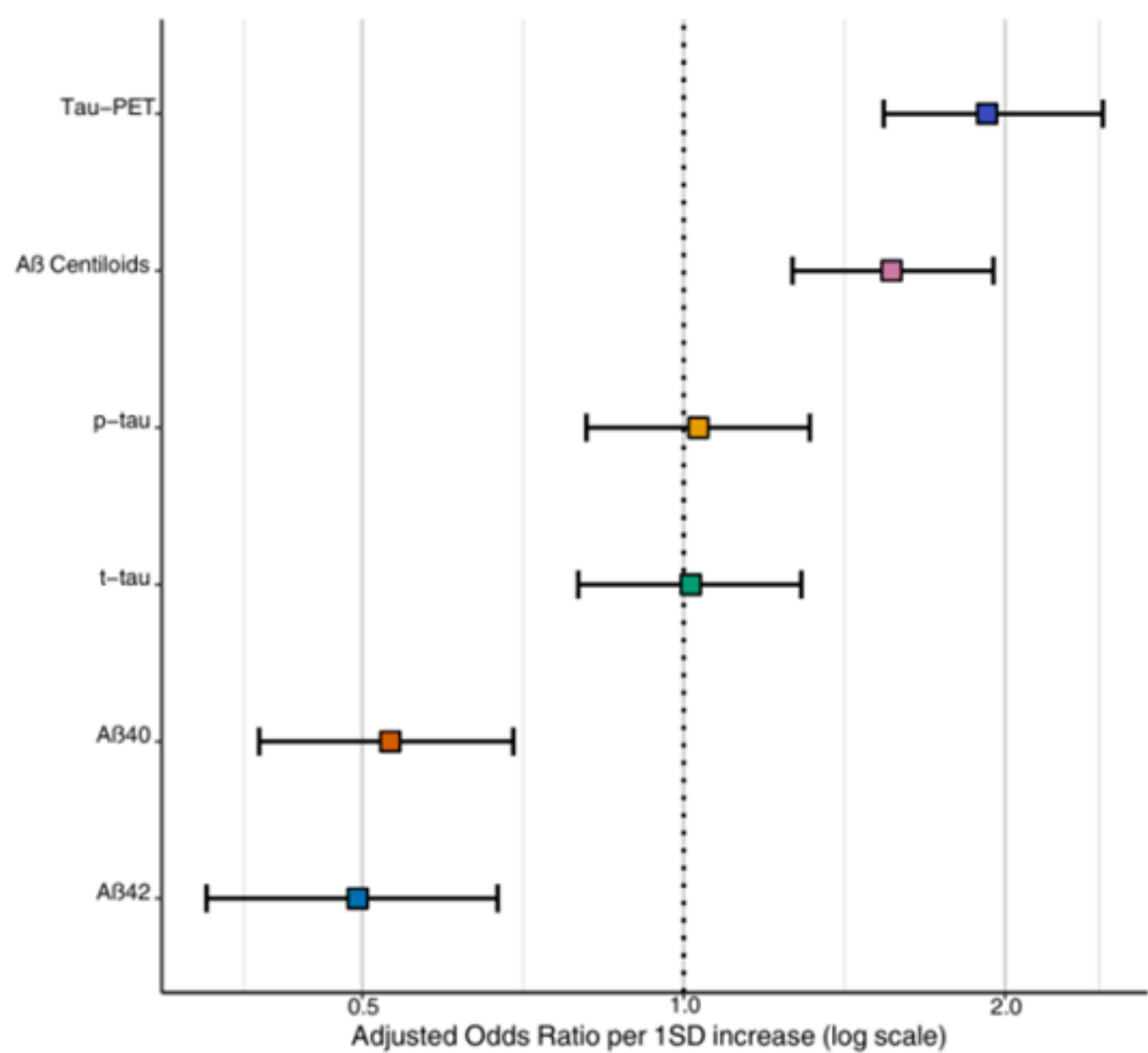


Figure 2. Biomarkers predicting medial temporal atrophy. Forest plot of adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the outcome $MTA \geq 2$ per 1 standard deviation (SD) increase in each biomarker (log scale). Adjusted for age, sex and APOE ϵ 4. Squares represent point estimates of ORs and horizontal lines indicate 95% CIs. The vertical dotted line denotes OR = 1.

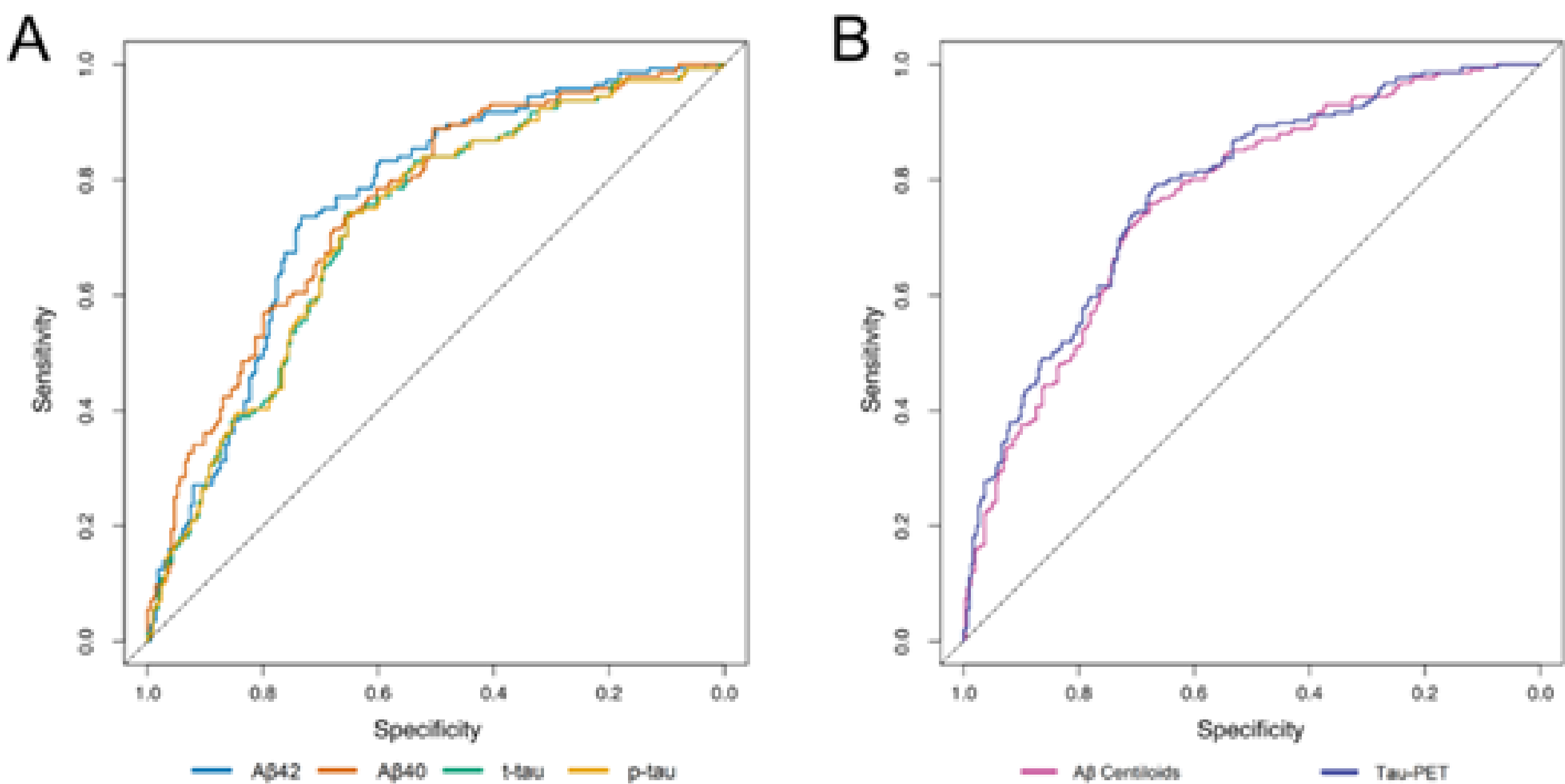


Figure 1. ROC curves of CSF and PET biomarkers for discriminating medial temporal atrophy. Receiver operating characteristic (ROC) curves showing the discrimination of $MTA \geq 2$ by biomarkers, with models adjusted for age, sex, and APOE ϵ 4 carrier status. (A) CSF biomarkers ($A\beta$ 42, $A\beta$ 40, t-tau, and p-tau). (B) PET biomarkers ($A\beta$ Centiloids and Tau-PET). Sensitivity is plotted against specificity; the diagonal dashed line indicates performance no better than chance.

Conclusion

In this cohort, meta-temporal tau-PET SUVR was the single biomarker most associated and most discriminative for hippocampal atrophy. $A\beta$ 42 performed best for identifying participants with hippocampal atrophy among CSF biomarkers. PET-based markers, particularly tau-PET, appeared more informative than CSF biomarkers for estimating hippocampal atrophy severity, supporting tau-PET as the main biomarker to differentiate hippocampal atrophy.

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