

Plasma brain-derived pTau217/BD-Tau ratio improves discrimination of Aβ-PET and tau-PET positivity compared with pTau217 alone

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Plasma pTau217 and its brain-derived counterpart (BD-pTau217) exhibited strong diagnostic performance for predicting both Aβ- and tau-PET positivity in an elderly Australian cohort. The novel BD-pTau217/BD-Tau ratio also showed strong performance for predicting Aβ-PET and significantly outperformed BD-pTau217 alone in predicting tau-PET.

INTRODUCTION

Plasma phosphorylated tau 217 (pTau217) accurately detects Amyloid-beta (Aβ) and tau-PET positivity, but variability in plasma Aβ42 measurement highlights the need for a high-throughput, robust biomarker for both Aβ- and tau-PET in research and clinical settings.

METHODS

The study included 500 participants across the AD continuum from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study (223 cognitively unimpaired, 171 Aβ+ mild cognitive impairment, and 104 Aβ+ AD).

Plasma samples were collected within 12 months of Aβ-PET and MK6240 tau-PET imaging. BD-pTau217, BD-Tau, pTau217, Aβ42, GFAP, and NfL were measured using research-use-only assays on the Beckman Coulter Dxl 9000 Immunoassay Analyzer.

Covariate-adjusted models (age, sex, APOE ε4) were evaluated using AUC for Aβ-PET positivity (Centiloid ≥25) and tau-PET positivity (meta-temporal SUVR ≥1.48). High tau burden was defined as temporoparietal SUVR in the top quartile (≥2.68).

RESULTS

The brain-derived pTau217 assays enhanced discrimination between biological staging groups, producing larger mean differences in biomarker levels than the original assays (Figure 1).

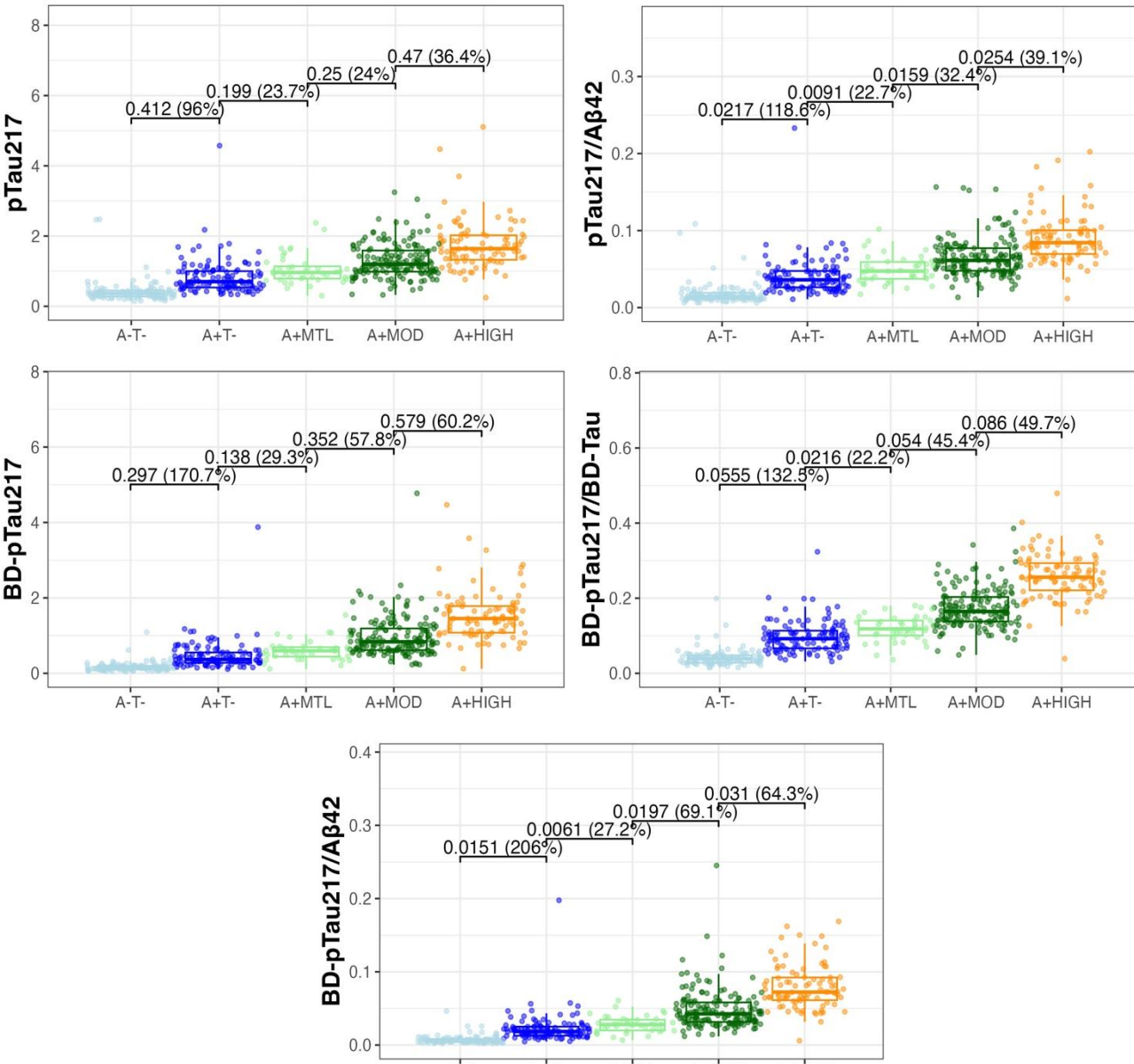


Figure 1: Box and whisker plot of biomarker values across biological disease stage.

The AUC value for the detection of Aβ-PET positivity for BD-pTau217 (0.960) was numerically higher, but not significantly greater than, for pTau217 (0.938, p=0.11).

RESULTS

Accounting for levels of BD-Tau within a novel BD-pTau217/BD-Tau ratio, the AUC value to detect Aβ-PET positivity was significantly higher than pTau217 alone (0.973 vs 0.938, p=0.037).

For tau-PET, BD-pTau217 significantly improved the AUC value compared to pTau217 alone (0.924 vs. 0.883, p<0.0001), whilst the BD-pTau217/BD-Tau ratio further increased the AUC (0.936, p=0.039).

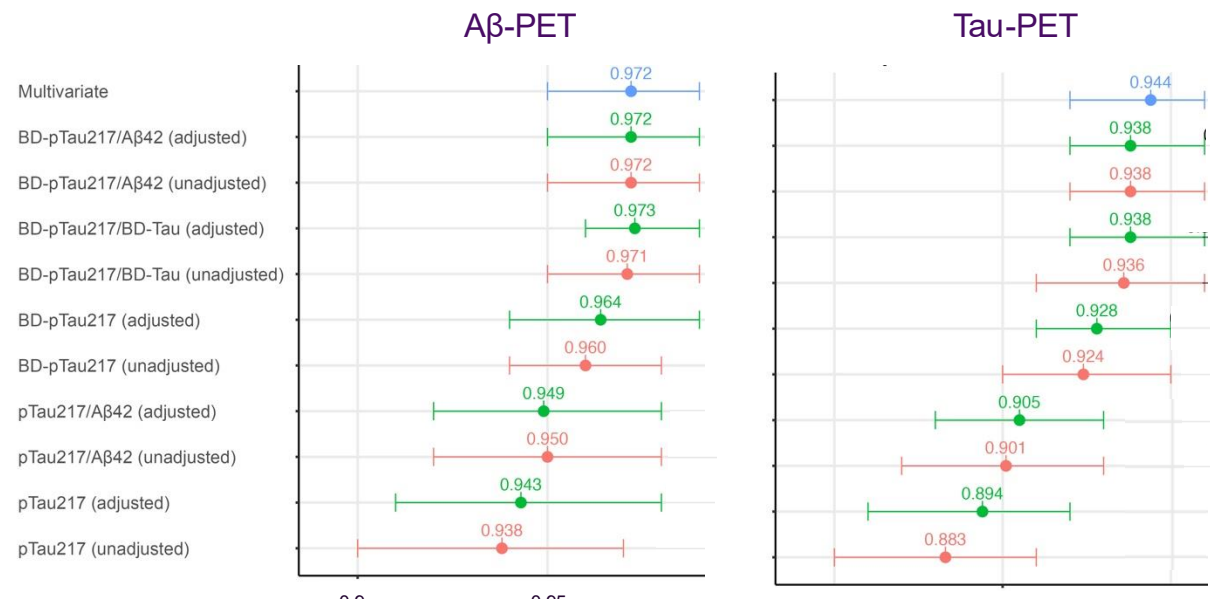


Figure 2: Plasma biomarker AUC to detect Aβ-PET (left) and Tau-PET (right). Aβ-PET values are the means from 1000 bootstraps to achieve ~62% Aβ-PET positive prevalence.

There were no differences in any biomarker between models adjusted for age, gender and APOE ε4 allele status, and models containing the biomarker alone.

RESULTS

Comparing all participants against those with high tau (A+T_{HIGH}), the BD-pTau217/BD-Tau ratio had a significantly higher AUC than the BD-pTau217/Aβ42 ratio (0.940 vs. 0.924, p=0.015), with the intermediate zone at 90% sensitivity and 90% specificity cutoffs reduced by half (4.4% vs. 8.8%).

Biomarker	Index	AUC (95%CI)	Indeterminate zone
pTau217	Youden's	0.849 (0.81 - 0.89)	13.60%
	Sens. & Spec. 85		31.40%
	Sens. & Spec. 90		44.0%
pTau217/Aβ42	Sens. & Spec. 95		
	Youden's	0.882 (0.85 - 0.92)	7.80%
	Sens. & Spec. 85		20.80%
BD-pTau217	Sens. & Spec. 90		30.40%
	Sens. & Spec. 95		
	Youden's	0.906 (0.87 - 0.94)	0.80%
BD-pTau217 /BD-Tau	Sens. & Spec. 85		16.0%
	Sens. & Spec. 90		27.0%
	Sens. & Spec. 95		
BD-pTau217 /Aβ42	Youden's	0.94 (0.91 - 0.97)	0%
	Sens. & Spec. 85		4.0%
	Sens. & Spec. 90		12.0%
BD-pTau217 /Aβ42	Sens. & Spec. 95		0%
	Youden's	0.924 (0.9 - 0.95)	8.80%
	Sens. & Spec. 90		20.20%
/BD-Tau	Sens. & Spec. 85		
	Sens. & Spec. 90		
	Sens. & Spec. 95		

CONCLUSIONS

With increased performance for tau-PET and very high AUC values for Aβ-PET, the BD-pTau217 assay demonstrated potential for scalable assessment of AD pathology in research, and potentially in clinical settings.

Both BD-pTau217/Aβ42 and BD-pTau217/BD-Tau ratios separate AD pathology well, however the BD-pTau217/BD-Tau ratio performs better to separate late-stage disease.

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Table 1: Plasma biomarker AUC and intermediate zone proportion to separate A+HIGH from all other participants.