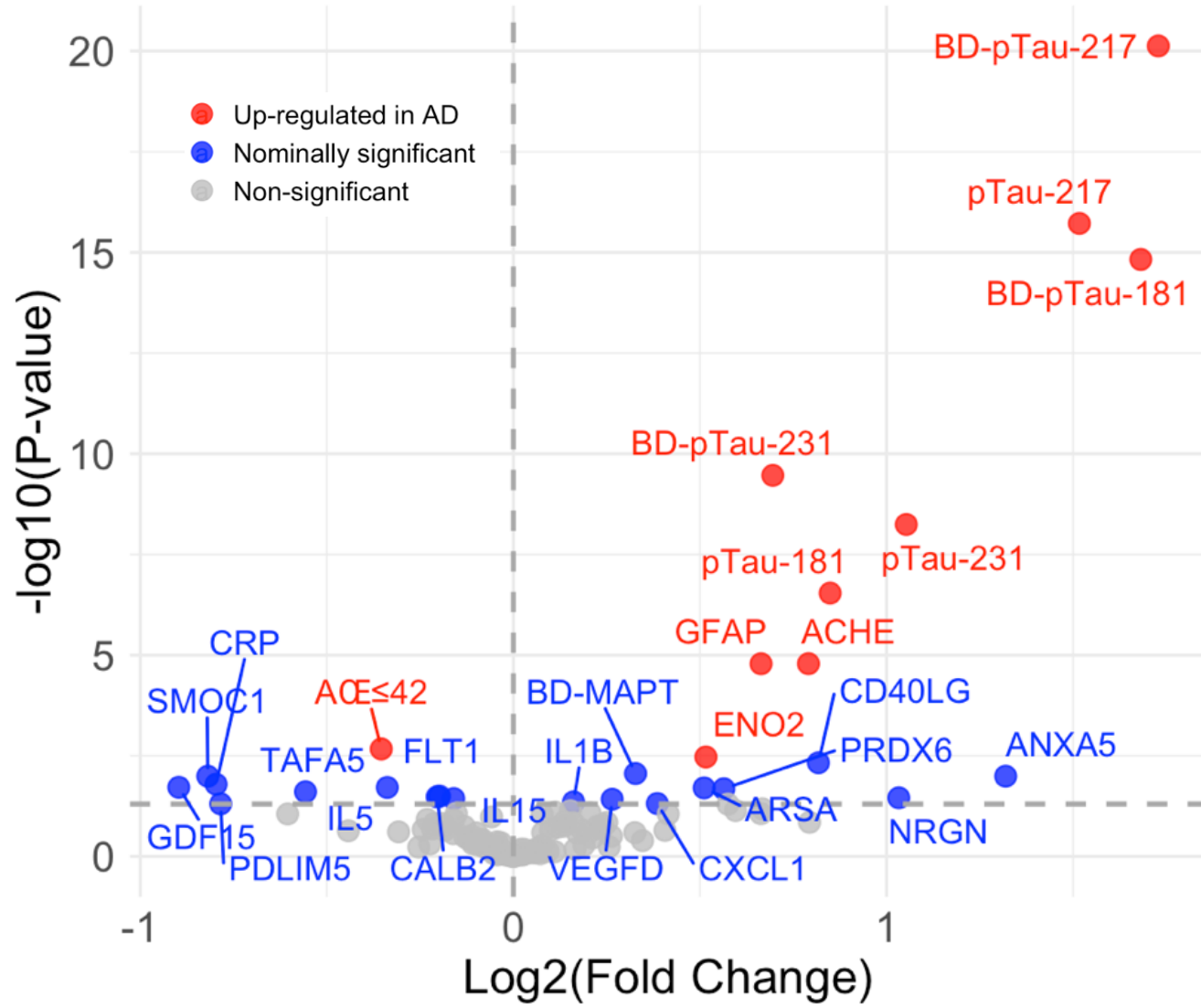


INTRODUCTION

- **Plasma phosphorylated tau (p-Tau) biomarkers**, particularly p-Tau217, show high accuracy for detecting **Alzheimer’s disease (AD) pathology**.
 - However, p-Tau217 can also be peripherally derived and elevated in other neurological disorders such as ALS.
 - **Brain-derived (BD) p-Tau217** is a promising biomarker that selectively measures central nervous (CNS) system derived p-Tau217, potentially improving specificity for AD pathology.
- Study aims
- Identify significantly upregulated biomarkers for AD pathology in a cohort with *post-mortem* confirmed neuropathology.
 - Compare the diagnostic performance of brain-derived phosphorylated tau biomarkers with their plasma counterparts.

RESULTS

Figure 1. Differential protein expression in AD and receiver operating characteristic (ROC) curves of upregulated biomarkers.
AD: CERAD C with Braak V-VI; non-AD: CERAD none



In **Figure 2a** BD p-Tau biomarkers (BD p-Tau217: $\rho = 0.63$, BD p-Tau181: $\rho = 0.58$, BD p-Tau231: $\rho = 0.51$) showed stronger correlations with plaque stage than total p-Tau versions (p-Tau217: $\rho = 0.58$, p-Tau181: $\rho = 0.42$, p-Tau231: $\rho = 0.46$). Steiger’s tests confirmed **significantly greater associations between BD p-Tau markers and CERAD stage** (p-Tau217, $z = 4.24$; p-Tau181, $z = 5.41$; p-Tau231, $z = 4.48$; $p < 0.001$).

In **Figure 2b**, BD p-Tau biomarkers (BD p-Tau217: $\rho = 0.65$, BD p-Tau181: $\rho = 0.59$, BD p-Tau231: $\rho = 0.50$) showed stronger correlations with tangle stage total p-Tau versions (p-Tau217: $\rho = 0.60$, p-Tau181: $\rho = 0.48$, p-Tau231: $\rho = 0.50$). Steiger’s tests confirmed **significantly greater associations between BD p-Tau markers and Braak stage** (p-Tau217, $z = 4.39$; p-Tau181, $z = 4.04$; p-Tau231, $z = 3.22$; $p < 0.001$).

Figure 2. Correlations of BD p-Tau and plasma p-Tau biomarkers with plaque and tangle pathology

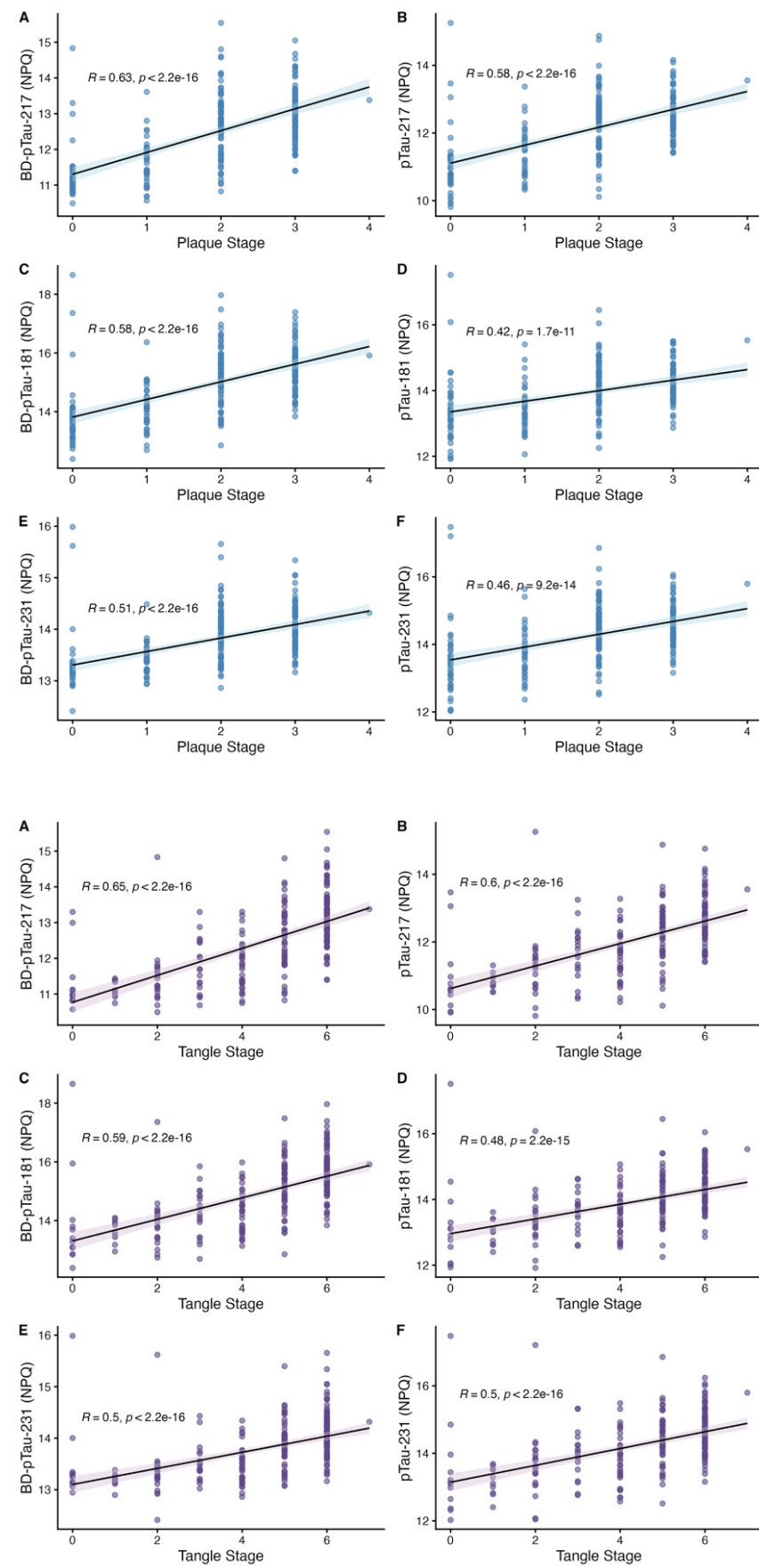
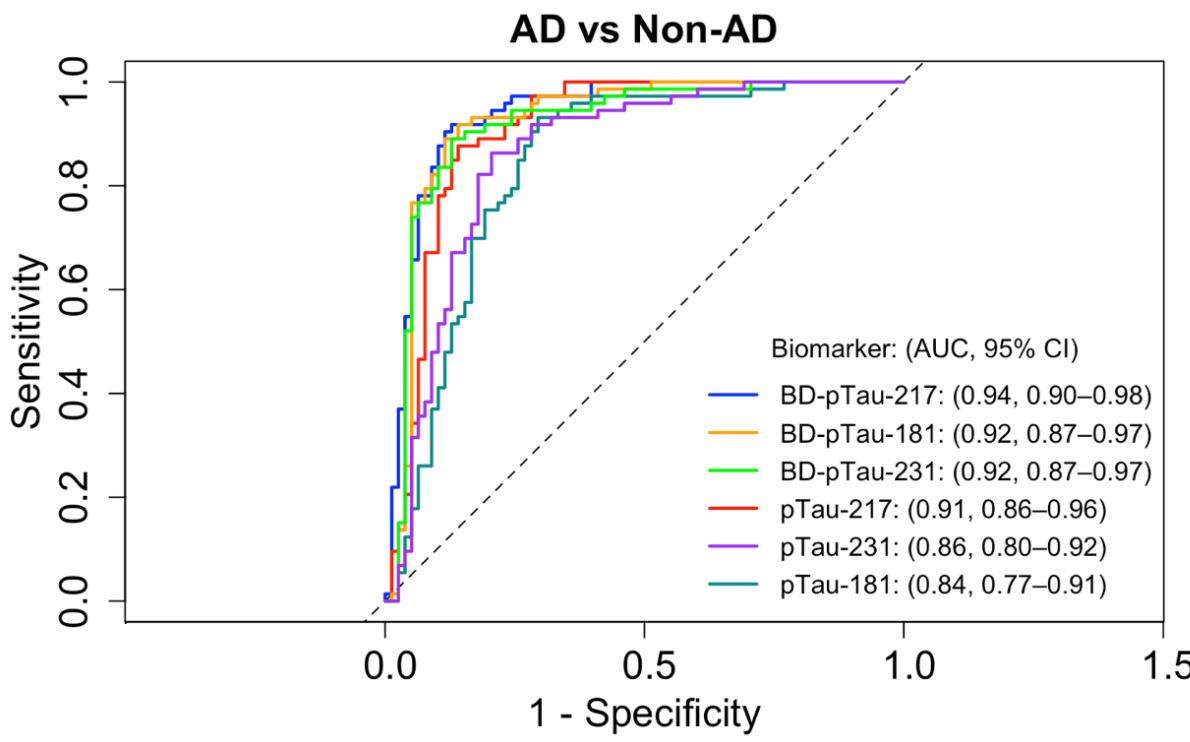
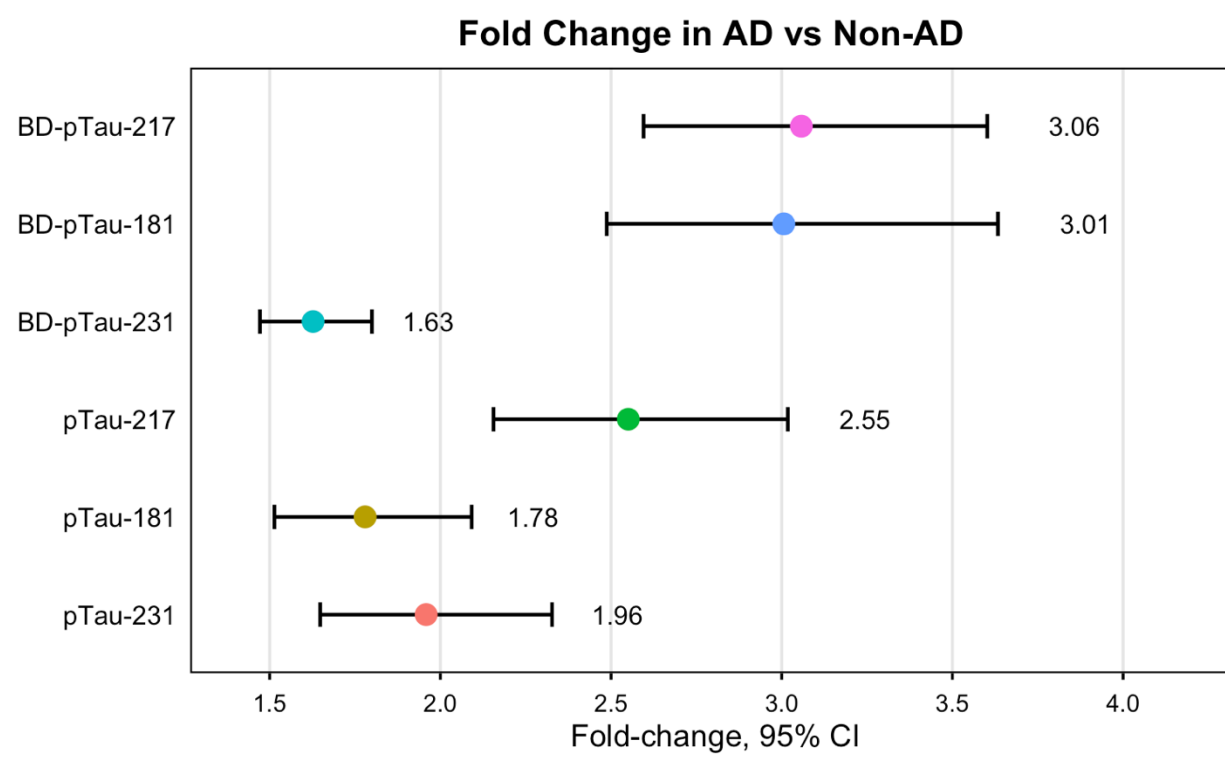


Figure 3. Diagnostic accuracy and mean fold-change in biomarker levels.
AD: CERAD C with Braak V-VI; non-AD: CERAD none



In **Figure 3a** BD p-Tau217 and BD p-Tau181 demonstrated strong accuracy in distinguishing AD from non-AD.

Pairwise DeLong tests and Benjamini-Hochberg correction confirmed significantly higher AUCs for BD versus total p-Tau plasma biomarkers ($p_{adj} = 0.011, 0.001, 0.002$) for BD p-Tau217, 181, 231, respectively.



In **Figure 3b** fold-change analyses indicated higher elevations for BD p-Tau217 (3.06) and BD p-Tau181 (3.01) compared with p-Tau217 (2.55) and p-Tau181 (1.78) in AD versus non-AD.

METHODS

Study Design:

This was a cross-sectional study evaluating the relationship between fluid biomarkers and neuropathologically defined Alzheimer's disease pathology. Biomarker performance was assessed for the detection of amyloid plaque and neurofibrillary tangle burden.

Participants / Samples:

- The study included 257 participants from the University of California, Irvine Alzheimer Disease Research Center (mean age 81.1 ± 11.4 years; 54.9% female) with available clinical, plasma, and autopsy data.
- Plasma samples were collected ante-mortem, with a mean assay-to-autopsy interval of 2.9 ± 2.8 days. Age at death and sex were included as covariates.
- Plasma samples were analyzed with NULISA™ CNS-120 (Alamar Biosciences) at the Fluid Biomarker Program at Banner Sun Health Research Institute (BSHRI)

Statistical Analysis:

- Associations between brain-derived and plasma p-Tau217, p-Tau181, p-Tau231 and neuropathological outcomes were evaluated using Spearman rank correlations.
- Differential expression analyses were performed to identify biomarker differences across neuropathological groups, driving downstream analyses. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) analysis.
- DeLong's tests were used to compare ROC AUCs between biomarkers, and Steiger's tests were used to compare correlated correlation coefficients. All statistical analyses were conducted in R (version 2025.05.1+513).

	Overall (N=257)
Age at death, years	81.12 (11.37)
Female, n (%)	116 (45.1%)
Time between death and autopsy, mean (SD)	2.91 (2.81)
CERAD Plaque Score, n (%)	
None	41 (16%)
Stage A	37 (14.4%)
Stage B	81 (31.5%)
Stage C	79 (30.7%)
NA	19 (7.4%)
Braak Tangle Stage, n (%)	
I	10 (3.9%)
II	22 (8.6%)
III	18 (7%)
IV	33 (12.8%)
V	54 (21%)
VI	89 (34.6%)
NA	31 (12.1%)

Table 1. Demographics of the UCI Neuropathological cohort

CONCLUSION / DISCUSSION

Implications

- BD p-Tau biomarkers, particularly BD p-Tau217 and BD p-Tau181, demonstrate **superior discrimination of AD pathology** compared with conventional total plasma p-Tau biomarkers.
- The strong associations between BD p-Tau measures and both amyloid plaque and neurofibrillary tangle burden suggest that these biomarkers may more closely reflect underlying AD neuropathology.
- Notably, p-Tau181 achieves similar performance to p-Tau217 when using the BD-tau version, supporting BD p-Tau biomarkers’ potential utility in research and clinical assessment of AD.

Future Directions

- Assess the longitudinal performance of BD p-Tau biomarkers for predicting cognitive decline and disease progression.
- Evaluate multi-biomarker models using BD p-Tau biomarkers in combination with other AD biomarkers to improve diagnostic accuracy and risk stratification.
 - Significant changes in GFAP, ACHE, ENO2 and several biomarkers were also observed in the neuropathological cohort (**Figure 1**)
- Investigate the role of BD p-Tau biomarkers in clinical trials for early disease detection and therapeutic monitoring.

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