Head-to-head comparisons of cross-sectional and longitudinal diagnostic performance of plasma p-tau/Aβ ratios in Alzheimer's disease

Mingxing Jiang[1,2], Laihong Zhang[2], Jiayi Zhu[2], Guoyu Lan[2], and Tengfei Guo[2]

[1] *Shenzhen Medical Academy of Research and Translation, Shenzhen, 518132, China*

[2] *Institute of Neurological and Psychiatric Disorders, Shenzhen Bay Laboratory, Shenzhen, 518132, China*

Background

- Recent studies suggest that combining plasma phosphorylated tau (p-tau) and β-amyloid (Aβ) biomarkers may improve the accuracy and reduce the percentage of intermediate zone in detecting Alzheimer's disease (AD).
- However, the cross-sectional and longitudinal concordance and discordance of plasma p-tau/Aβ ratio with Aβ positron emission tomography (PET) positivity are not fully understood.
- This study aimed to evaluate the cross-sectional and longitudinal diagnostic performance of combined plasma p-tau and Aβ biomarkers for detecting Aβ-PET positivity in AD.

Methods

Cohorts

- **GHABS (**N=357, Chinese older adults, with 229 Aβ- and 128 Aβ+**)**
- **ADNI (**N=326, Caucasian individuals, with 212 Aβ- and 114 Aβ+**)**

Biomarkers

- Plasma p-tau181, p-tau217, Aβ42 and Aβ40 measured across different analytical platforms, including Quanterix HD-X, Lumipulse G1200, Roche Elecsys , and C2N PrecivityAD2.

Approach

- Two-cutoff framework defined negative, intermediate and positive group.
- Upper cutoff determined by maximizing specificity at a fixed sensitivity(GHABS:95%; ADNI:92%) and lower cutoff determined by maximizing sensitivity at a fixed specificity(GHABS:95%; ADNI:92%).
- Aβ PET as reference standard
- Cross-sectional and longitudinal analysis

Results

Figure 1. Two-cutoff approach for predicting Aβ PET positivity

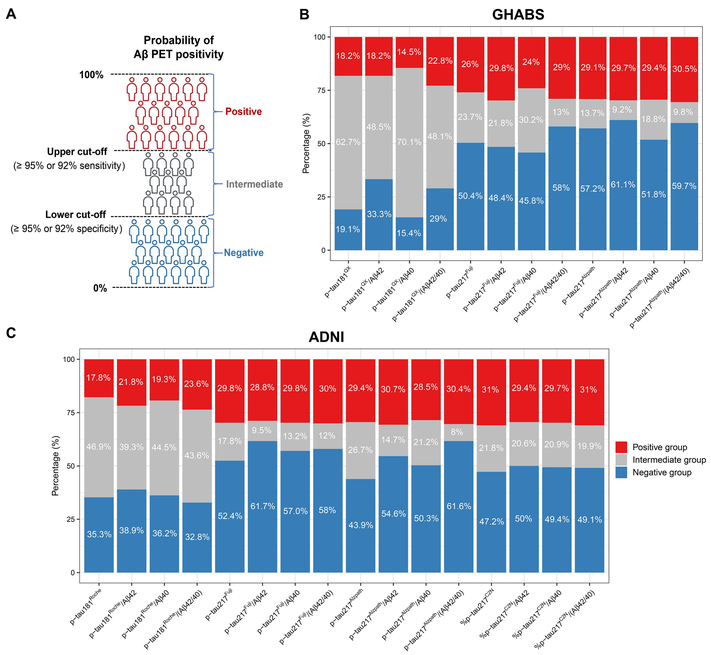
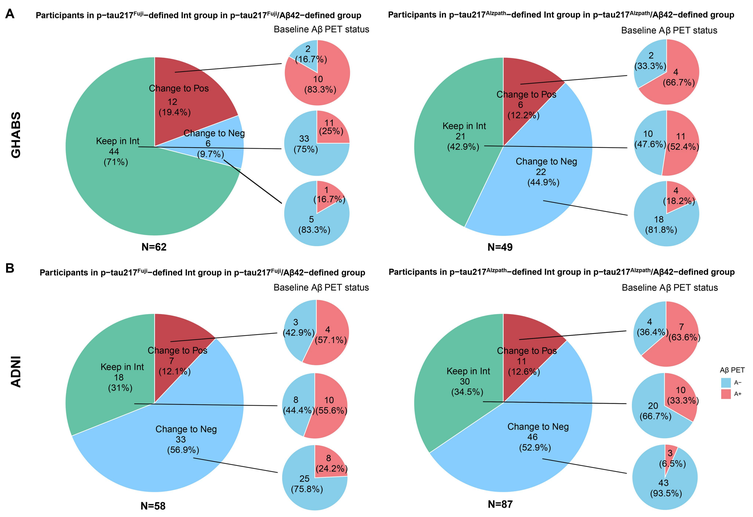
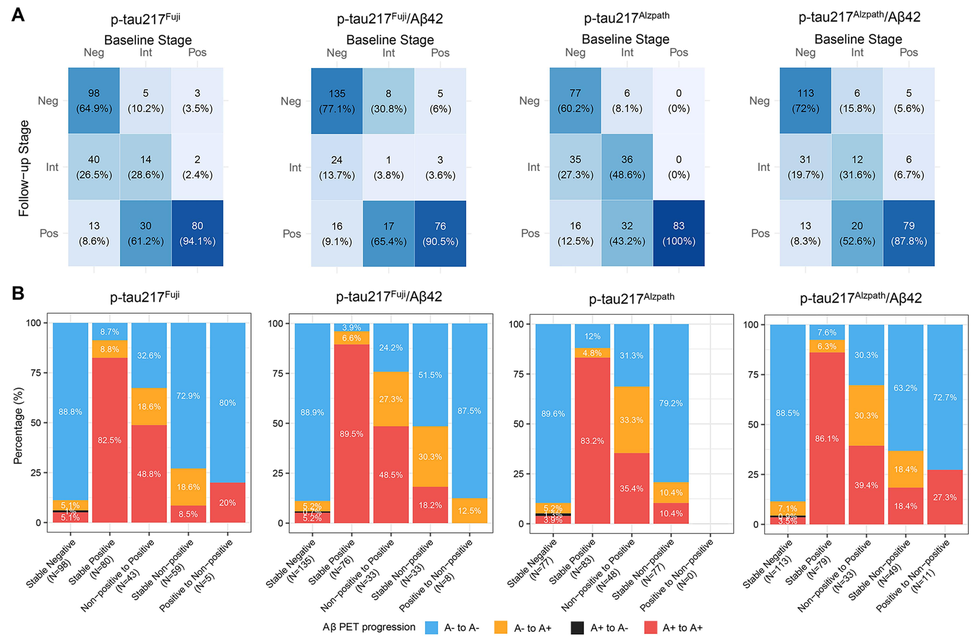


Figure2. Reclassification of participants in the p-tau217–defined intermediate group using the p-tau217/Aβ42 ratio and corresponding Aβ PET status



- **Finding 1:** Combining plasma p-tau (p-tau181, p-tau217) biomarkers with Aβ42 or the Aβ42/40 ratio reduced the proportion of intermediate zone under the two-cutoff approach relative to single biomarkers (Figure 1).
- **Finding 2:** The p-tau217/Aβ42 ratio showed stronger agreement with Aβ-PET positivity than p-tau217 alone. Among individuals classified as p-tau217/Aβ42-positive but p-tau217-intermediate, 57.1%–83.3% were Aβ-PET positive, while 75.8%–93.5% of those classified as p-tau217/Aβ42-negative were Aβ-PET negative (Figure 2).
- **Finding 3:** Individuals classified as positive at baseline remained highly stable over time (Figure 3A), and most of the Stable Positive and Non-positive to Positive cases defined by p-tau217/Aβ42 were Aβ-PET positive, whereas Stable Negative and Stable Non-positive individuals were substantially Aβ-PET negative (Figure 3B).

Figure 3. Longitudinal diagnostic performance of plasma p-tau217 and the p-tau217/Aβ ratio in the ADNI cohort.



- Longitudinally, participants were retrospectively categorized into five longitudinal trajectory profiles based on plasma p-tau217 and p-tau217/Aβ42 status classifications at both baseline and follow-up visits: Stable Negative, Stable Non-positive, Non-positive to Positive, Stable Positive, and Positive to Non-positive. Participants classified as either negative or intermediate were collectively referred to as "Non-positive".

Conclusion

- Combining plasma p-tau with Aβ42 or the Aβ42/40 ratio reduced the intermediate zone under the two-cutoff framework.
- Plasma p-tau217/Aβ42 showed stronger agreement with Aβ-PET positivity than p-tau217 alone.
- Longitudinally, baseline p-tau217/Aβ42-positive individuals remained highly stable, showing strong concordance with follow-up Aβ-PET status.

ID: #2892
Email:
jiangmingxing@smart.org.cn